Health Evidence Review Commission's Value-based Benefits Subcommittee

March 9, 2017

9:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
March 9, 2017
9:00am - 1:00pm
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
A working lunch will be served at approximately 12:00 PM
All times are approximate

I. Call to Order, Roll Call, Approval of Minutes – Kevin Olson **9:00 AM**

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman **9:05 AM**
A. Errata
B. Information desired for May review of opioid/back pain changes

III. Straightforward/Consent agenda – Ariel Smits, Cat Livingston **9:15 AM**
A. Consent table
B. Minor newborn conditions
C. Screening colonoscopy with polyp removal
D. Straightforward Coding Changes--Injuries to Major Blood Vessels
E. Preventive services guideline lead screening edits

IV. 2018 Biennial Review **9:25 AM**
A. Prioritization of novel treatments with marginal clinical benefit, low cost-effectiveness and/or high cost

Break **10:30 AM**

V. New discussion items **10:45 AM**
A. Pharmacogenetics testing for medications for psychiatric disorders
B. Pharmacist medication management guideline
C. Breast reduction for macromastia as treatment for neck and back pain
D. Elective surgery guideline and electronic cigarettes
E. Non-specific pain diagnoses
F. MRI for MS progression

VI. Public comment **12:55 PM**

VII. Adjournment – Kevin Olson **1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on March 9, 2017

For specific coding recommendations and guideline wording, please see the text of the 2/2/17 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 10/1/2017)

- Several dental procedures were added to covered lines
- Various straightforward coding changes were made
- Procedure codes for fecal microbiota transplant were added to a covered line with a new guideline to clarify coverage
- Procedure codes for cholecystectomy were added to the pancreatitis line and removed from the intestinal ileus line
- Limited coverage for tympanostomy tubes and adenoidectomy was added for high-risk children with hearing loss due to chronic otitis media older than age 5, with coverage limited through age 7 in the chronic otitis media with effusion guideline
- Adenoidectomy procedure codes were added to the covered line for hearing loss in children age 5 and under to clarify coverage

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Digital breast tomosynthesis (3D mammography) for breast cancer screening in average-risk women was considered for inclusion on the Prioritized List, but was found to have a lack of evidence to support use and was kept on the Services Recommended for Non-Coverage Table
- No changes were made to the bariatric surgery guideline section regarding marijuana use

RECOMMENDED GUIDELINE CHANGES (effective 10/1/2017)

- The dental guideline regarding wisdom tooth extraction was revised to clarify coverage
- The guideline defining significant injuries to joints was modified to include meniscal injuries
- A new guideline was adopted to define cholecystitis

2018 BIENNIEAL REVIEW CHANGES (effective 1/1/2018)

- Two lines with injuries to major blood vessels were merged and codes from a third line were moved to the new line to consolidate all diagnosis and treatment codes for major blood vessel injuries

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
February 2, 2017
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Susan Williams, MD, Vice-Chair (via phone); Mark Gibson; Irene Croswell, RPh (via phone until 10:45, then in person); Holly Jo Hodges, MD (via phone).

Members Absent: Vern Saboe, DC; Gary Allen, DMD; David Pollack, MD.

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Denise Taray, RN; Wally Shaffer, MD; Daphne Peck (via phone).

Also Attending: Jesse Little and Kim Wentz, MD, MPH, (Oregon Health Authority); Adam Obley, MD, MPH (OHSU Center for Evidence-based Policy), Scott Pohlman, Hologic; Chandler Schaab and Jennifer Valley (Stoney Girl Gardens); Cindy Fletcher (Komen Oregon and SW Washington).

- **Roll Call/Minutes Approval/Staff Report**

  The meeting was called to order at 8:00 am and roll was called. Minutes from the November 10, 2016 VbBS meeting were reviewed and approved without changes.

  Taray summarized a letter from the Oregon Pain Commission discouraging the Health Evidence Review Commission (HERC) from using a pain scale in guidelines, due to the subjective nature of a patient's scoring. A patient should not be denied a therapy because he or she gave a lower subjective pain score. Functional measures are preferred to be used to determine how much the pain is affecting an individual.

  Smits reviewed the most recently published errata; there was no discussion.

  Smits pointed out the final changes made to the Prioritized List (code changes and guideline changes) around sacroiliac joint fusion which were highlighted in the November 2016 minutes and had been previously approved by the VbBS/HERC leadership. These changes were slightly more extensive than what the VbBS had instructed staff to do, but were felt to be within the intent of the VbBS and no further changes were suggested.

- **Topic: Advisory Panel Reports**

Discussion: Smits pointed out the Oral Health Advisory Panel (OHAP) meeting minutes in the packet. There was a separate document outlining the suggested changes to the Prioritized List from OHAP. There was no discussion about these changes.

Recommended Actions:

1) Effective October 1, 2017
    a. Add K02 series (Dental caries) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    b. Add D7210 (Surgical removal of erupted tooth requiring removal of bone and/or sectioning of tooth, and including elevation of mucoperiosteal flap if indicated) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    c. Modify GN34 as shown in Appendix A
2) Effective January 1, 2018
    a. Add CDT D6100 (Implant removal, by report) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    b. Add D5221-D5222 (Immediate partial denture – resin base) to line 457 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES) and remove from line 594 DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH) Treatment: ADVANCED RESTORATIVE-ELECTIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS).

MOTION: To approve the recommendations stated in the OHAP recommendations. CARRIES 5-0.

- **Topic: Straightforward/Consent Agenda**

Discussion: Smits said a question had been raised about the CPT 44300 code entry (Placement, enterostomy or cecostomy, tube open (eg, for feeding or decompression)) and requested that this code not be included in the vote for this section. Staff will work to clarify the recommendation on this code and bring back to a future meeting. There was no further discussion about the consent agenda items.

Recommended Actions:

1) Add CPT 41015-41018 (Extraoral incision and drainage of abscess, cyst, or hematoma of floor of mouth) to line 210 SUPERFICIAL ABSCESSES AND CELLULITIS

2) Add CPT 14301 (Adjacent tissue transfer or rearrangement, any area; defect 30.1 sq cm to 60.0 sq cm) to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE
3) Add CPT 15734 (Muscle, myocutaneous, or fasciocutaneous flap; trunk) to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE
4) Add CPT 43270 (Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s)) to line 60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
5) Remove ICD-10 K51.4 (Inflammatory polyps of colon without complications) from line 32 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE and add to line 170 ANAL, RECTAL AND COLONIC POLYPS
6) Add CPT 43270 (Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s)) to line 60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
7) Add CPT 44346 (Revision of colostomy; with repair of paracolostomy hernia) to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE
8) Remove CPT 21210 (Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)) from line 305 CLEFT PALATE AND/OR CLEFT LIP
9) Add ICD-10 Z15.01 (Genetic susceptibility to malignant neoplasm of breast) and Z15.02 (Genetic susceptibility to malignant neoplasm of ovary) to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
10) Add CPT 43281-43283 (Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplasty, when performed, with or without mesh; Laparoscopy, surgical, esophageal lengthening procedure (eg, Collis gastroplasty or wedge gastroplasty)) to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 5-0.

- **Topic: 2018 Biennial Review: Injuries to Blood Vessels**

Discussion: Smits introduced the staff summary document and recommendations. The general consensus of the VbBS was to create one line for major blood vessel injuries as a cleaner solution. Williams said there are very different outcomes for injuries to major vessels of the abdomen/chest due to the high risk of death or major morbidity from these injuries. However, it was brought up that repair of major thoracic/abdominal vessels are effective when there is the ability to stabilize the patient long enough to do such repair; therefore the repair is effective when done. The decision was to create one line for all major blood vessel injuries.

Livingston pointed out that a few minor blood vessel injury codes were listed for inclusion on line 82 in the staff recommendation document. It was agreed that staff should review all the codes listed for inclusion on the new line and suggest moving superficial vessel injuries to a lower line. Staff will bring back these recommendations as a straightforward item to the March VbBS meeting.

Recommended Actions:

These changes are all effective January 1, 2018

1) Add CPT 35207 (Repair blood vessel, direct; hand, finger) to line 294 CRUSH AND OTHER INJURIES OF DIGITS
2) Change the title of line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME~~; INJURIES TO BLOOD VESSEL(S) OF THE NECK~~
    a. Remove the following ICD-10 codes from line 135 and leave on other current line(s):
        i. S45 (Injury of blood vessels at shoulder and upper arm level)
        ii. S55 (Injury of blood vessels at forearm level)
        iii. S65.0-S65.3, S65.8-S65.9 (Injury of blood vessels at wrist and hand level)
        iv. S75 (Injury of blood vessels at high and thigh level)
        v. S85 (Injury of blood vessels at lower leg level)
        vi. S95 (Injury of blood vessels at ankle and foot level)
    b. Remove the following blood vessel repair CPT codes from line 135:
        i. 35206 Repair blood vessel, direct; upper extremity
        ii. 35207 Repair blood vessel, direct; hand, finger
        iii. 35236 Repair blood vessel with vein graft; upper extremity
        iv. 35266 Repair blood vessel with graft other than vein; upper extremity
        v. 35521 Bypass graft, with vein; axillary-femoral
        vi. 37618 Ligation, major artery (eg, post-traumatic, rupture); extremity
3) Merge line 281 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY and line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES and prioritize the new line to line 82. The title of the new line will be 82 INJURY TO MAJOR BLOOD VESSELS ~~OF EXTREMITIES AND NECK~~
    a. Include all ICD-10 and CPT codes currently appearing on lines 82 and 281
    b. Remove the following ICD-10 codes from line 135 and add to new line 82:
        i. S09.0XXA, S09.0XXD (Injury of blood vessels of head, not elsewhere classified)
        ii. S27.9XXA, S27.9XXD (Injury of unspecified intrathoracic organ)
        iii. S35.00XA, S35.00XD, S35.01XA, S35.01XD, S35.02XA, S35.02XD, S35.09XA, S35.09XD (injury of abdominal aorta)
        iv. S35.10XA, S35.10XD, S35.11XA, S35.11XD, S35.12XA, S35.12XD, S35.19XA, S35.19XD (injury of inferior vena cava)
        v. S35.211A, S35.211D, S35.212A, S35.212D, S35.218A, S35.218D, S35.219A, S35.219D, S35.221A, S35.221D, S35.222A, S35.222D, S35.228A, S35.228D, S35.229A, S35.229D, S35.231A, S35.231D, S35.232A, S35.232D, S35.238A, S35.238D, S35.239A, S35.239D, S35.291A,

S35.291D, S35.292A, S35.292D, S35.298A, S35.298D, S35.299A, S35.299D (injury of celiac/inferior mesenteric/superior mesenteric artery)

vi. S35.311A, S35.311D, S35.318A, S35.318D, S35.319A, S35.319D, S35.321A, S35.321D, S35.328A, S35.328D, S35.329A, S35.329D, S35.331A, S35.331D, S35.338A, S35.338D, S35.339A, S35.339D, S35.341A, S35.341D, S35.348A, S35.348D, S35.349A, S35.349 (injury of portal/splenic/superior mesenteric/inferior mesenteric vein)

vii. S35.401A, S35.401D, S35.402A, S35.402D, S35.403A, S35.403D, S35.404A, S35.404D, S35.405A, S35.405D, S35.406A, S35.406D, S35.411A, S35.411D, S35.412A, S35.412D, S35.413A, S35.413D, S35.414A, S35.414D, S35.415A, S35.415D, S35.416A, S35.416D, S35.491A, S35.491D, S35.492A, S35.492D, S35.493A, S35.493D, S35.494A, S35.494D, S35.495A, S35.495D, S35.496A, S35.496D (injury of renal artery/vein)

viii. S35.50XA, S35.50XD, S35.511A, S35.511D, S35.512A, S35.512D, S35.513A, S35.513D, S35.514A, S35.514D, S35.515A, S35.515D, S35.516A, S35.516D, S35.531A, S35.531D, S35.532A, S35.532D, S35.533A, S35.533D, S35.534A, S35.534D, S35.535A, S35.535D, S35.536A, S35.536D (Injury of iliac artery/vein, uterine artery/vein, other vessels of lower abdomen or pelvis)

c. Remove ICD-10 S65.4 (injury of blood vessel of thumb) and S65.5 (injury of blood vessel of finger) from line 82
    i. Remain on line 294 CRUSH AND OTHER INJURIES OF DIGITS

MOTION: To approve the code change, line name changes, and line merging recommendations as presented. CARRIES 5-0.

- **Topic: 2018 Biennial Review: Secondary and Ill Defined Malignancies**

Discussion: Smits reviewed the summary document. There was discussion about whether it was more appropriate to code for the primary cancer or for the distant metastases. The answer appears to depend on what is being treated. If the primary cancer is being treated with surgery, chemotherapy, etc. then that diagnosis code is used. If a distant metastases is being treated with radiation, then frequently the diagnosis code for the metastasis is used. For OHP, Taray said when a claim has both the diagnosis code for the primary cancer as well as the code for the metastasis, the claims system only sees the first code and will deny the claim if that code is for a secondary metastasis on line 595 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS.

The discussion turned to the issue of the effectiveness of the treatment for the secondary cancer, which depends on the primary cancer. For example, colon cancer metastatic to the lung has a very different treatment effectiveness and prognosis than breast cancer metastatic to the lung. It is hard to lump secondary cancers metastatic to an organ onto the

same line as the primary cancer of that organ, because of the very different biology of that cancer, with very different treatments and outcomes. There is also cancers with unknown primaries, which have treatment paradigms of their own.

Gingerich said a recent data run found many claims for radiation therapy and other types of therapies for diagnoses on line 595. If treatment were for palliation (e.g. radiation to a painful bony metastasis), then the palliative care statement of intent applies. HSD staff said the Statement of Intent (SOI) 1: Palliative Care cannot be entered in the claims system, so these claims typically denied.

Taray said many of the diagnosis codes on line 595 are very vague and could be put in the HSD Undefined File. Some codes might also be put in the Diagnostic Workup File to allow some testing to try to get a better diagnosis.

Olson suggested creating a line for cancers of unknown primary; there are studies that look at outcomes for patients in this category. The very vague malignant neoplasm diagnoses might also go on such a line.

Williams said some of the diagnosis codes on line 595 make sense to move, for example the head and neck lymph nodes diagnoses might go onto a head and neck cancer line. She advocated keeping line 595 for vague diagnosis and for rare cancers with very poor outcomes even with treatment, such as splenic cancer.

Olson suggested creating a small work group to look at the diagnoses on this line and decide which might be more appropriate to move to other lines. For example, the secondary bone cancer diagnoses might be appropriate to move to the bone cancer line to allow radiation therapy.

Wentz said no claims for diagnoses on line 595 get paid for unless they are appealed. The palliative care statement of intent cannot be added to the claims process, but can be taken into account during appeals.

There was some discussion that many of the claims for line 595 appear to be from radiation facilities. Treatment for painful bony metastases should be covered. The Commission does not want to create administrative barriers to this type of palliative care. There was some thought about making a line for palliative radiation. However, it was thought that it would take some time to create such a line, and it likely would not take effect until the next biennial review cycle in 2020. Taray said the Oregon Pain Commission had a workgroup looking at updating the Statement of Intent 1 language to make more clear which palliative care services were covered. This might help clarify coverage for palliation for diagnoses on line 595.

The subcommittee decided to have staff review codes on line 595 as well as denied claims to see what “low hanging fruit” could be easily addressed and bring back to a future

meeting. Staff may have discussions with Olson to facilitate addressing the most pressing issues regarding diagnoses on line 595 using the existing line structure.

Staff will also look into whether palliative radiation is being covered and, if not, what barriers need to be removed. One idea was to have staff consider moving bone metastases to the bone cancer line with a guideline limiting services to palliative radiation.

Recommended Actions:

1) Staff to work with Olson on addressing problematic diagnoses on line 595 and bringing back suggested changes to a future VbBS meeting

- **Topic: Coverage Guidance: Digital Breast Tomosynthesis (3D Mammography) for Breast Cancer Screening in Average-risk Women**

Discussion: Shaffer reviewed the summary document. Public testimony was heard from Scott Holman, from Hologic (manufacturer of Digital Breast Tomosynthesis (DBT)). Mr. Holman gave a handout on estimated cost saving for Medicaid with DBT. This handout included estimates of 20% of eligible Medicaid women getting screening and 25% of that group getting DBT would result in a $8.14 savings per woman screened (reducing cost of recall and cancer treatment).

Olson asked if there was evidence that breast cancer is actually detected earlier with DBT. Holman replied that yes, more low-stage cancers are found with DBT. Obley noted that there is no published literature showing change in stage of cancer detected with DBT. He noted that with minimal recall reduction (2.3%), costs actually increase by $5 per member per month (PMPM). Obley argued that if you take out reduced costs from earlier stage detection from the manufacturer model, then it is not cost savings in any scenario.

Holman said DBT is an improved version of mammography with lower false positives. Short-term reduction in costs from not having to investigate false positives is cost savings. He said 27 states currently cover DBT for Medicaid. He also noted that the Medicaid population has a lower rate of screening, so it is more important to have a more accurate mammogram when they are screened.

The VbBS decision was to accept the staff recommendation to continue to include DBT on the Services Recommended for Non-Coverage Table.

Recommended Actions:

1) Keep CPT 77063 (Screening digital breast tomosynthesis; bilateral) on the Services Recommended for Non-Coverage Table

MOTION: To approve the recommendations for no change. CARRIES 5-0.

- **Topic: Fecal Microbiota Transplant for Recurrent C Difficile Infection**

Discussion: Smits introduced the summary document. Livingston asked if there should be any wording in the proposed guideline about mode of administration. Smits responded that the evidence base used various modes of administration and at this time she did not recommend limiting it to any particular mode. This might change as the technology develops. The subcommittee decided to include the suggested guideline note.

Recommended Actions:

1) Add CPT 44705 (Preparation of fecal microbiota for instillation, including assessment of donor specimen) to line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING and remove from the Services Recommended for Non-Coverage Table
2) Add HCPCS G0455 (Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen) to line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING and remove from the Services Recommended for Non-Coverage Table
3) Adopt a new Guideline Note for line 150 as shown in Appendix B

MOTION: To approve the coding and guideline note changes as presented. CARRIES 5-0.

- **Topic: Coverage of Cholecystectomy for Gallstones**

Discussion: Smits reviewed the summary document. The group discussed whether to require 2 or 3 items for diagnosis of cholecystitis and decided that 2 was sufficient.

The group discussed whether to include biliary colic on the covered upper line. Gibson noted that the evidence for coverage of biliary colic was poor. Hodges said she did not agree with moving biliary colic alone without any other sign of problems to the covered line. Olson said there is no evidence about the natural history of what happens when recurrent biliary pain is not treated. The studies presented are all retrospective. Gibson suggested that the CCOs consider treatment of recurrent biliary colic as an exception.

The subcommittee felt that all biliary colic, including recurrent colic, should be included on the lower gallstone line. There was discussion about how to word this in the guideline; the decision was to change the name of the lower line to include “biliary colic.”

Recommended Actions:

1) Add the following cholecystectomy CPT codes to line 199 ACUTE PANCREATITIS for pairing with gallstone pancreatitis (ICD10 K85.1)
    a. 47562 (Laparoscopy, surgical; cholecystectomy)
    b. 47563 (Laparoscopy, surgical; cholecystectomy with cholangiography)
    c. 47564 (Laparoscopy, surgical; cholecystectomy with exploration of common duct)

d. 47600-47620 (Cholecystectomy)

2) Remove 47562 (Laparoscopy, surgical; cholecystectomy) from line 311 PARALYTIC ILEUS
3) Change the name of line 645 GALLSTONES WITHOUT CHOLECYSTITIS; BILIARY COLIC
4) Adopt a new guideline note for lines 59 and 645 as shown in Appendix B

MOTION: To approve the coding, line name change and guideline note changes as amended. CARRIES 5-0.

- **Topic: Meniscal Injuries**

Discussion: Smits introduced the summary document. Williams said she agreed with the staff recommendations. There was no other discussion.

Recommended Actions:

1) Guideline Note 98 was modified as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 5-0.

- **Topic: Chronic otitis media (COM) with hearing loss**

Discussion: Smits reviewed the summary document and staff recommendations.

Testimony was heard from Kim Wentz, MD, speaking as a pediatrician. She testified that the staff evidence review did not recognize the difficulty in measuring and detecting long-term outcomes on behavior, school performance, etc. in children. For children, short-term benefits are very important; hearing loss during a critical developmental period may have significant impact, including on cognitive and social development. Preventive treatment in kids has a much greater return on investment than preventive treatment in adults due to the developmental needs of kids. Medicaid children are already at a disadvantage due to issues around low income. Denying this treatment is another strike against them. This is one area where she recommends deferring the decision to ear-nose and throat doctors (ENTs), who are the experts. Wentz also said the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) component of Medicaid applies to children to age 21. She implied that EPSDT might require treatment of hearing loss from COM. She did note that the OHP EPSDT waiver does allow use of the Prioritized List. She added that pressure equalization (PE) tubes are a relatively low cost intervention (~$1100).

The subcommittee discussion centered on the lack of evidence of significant benefit of treatment. There was discussion about whether the guideline should specify that coverage is through age 7, to reflect the evidence base presented. Williams said such specification was not needed due to the very narrow group of children already included for coverage in the guideline. However, the majority felt that the evidence should be reflected in the

guideline and wording was added to specify that coverage was only through age 7. Because this benefit will be limited to children through age 7, the CPT codes for adenoidectomy for children age 12 and older were not added to line 450.

Additional edits were made to the guideline to clarify that adenoidectomy was included for children aged 4 and older (rather than over 3 years) with their second set of tubes.

There was minimal discussion about whether to allow adenoidectomy with the first set of PE tubes.

Recommended Actions:

1) Add adenoidectomy CPT codes to lines 316 HEARING LOSS - AGE 5 OR UNDER
    a. CPT 42830 Adenoidectomy, primary; younger than age 12
    b. CPT 42835 Adenoidectomy, secondary; younger than age 12
    c. Add tympanostomy tube placement codes to line 450 HEARING LOSS - OVER AGE OF FIVE
        i. CPT 69433 Tympanostomy (requiring insertion of ventilating tube), local or topical anesthesia
        ii. CPT 69436 Tympanostomy (requiring insertion of ventilating tube), general anesthesia
    d. Add adenoidectomy codes to line 450 HEARING LOSS - OVER AGE OF FIVE for young children
        i. CPT 42830 Adenoidectomy, primary; younger than age 12
        ii. CPT 42835 Adenoidectomy, secondary; younger than age 12
    e. Guideline Note 51 was amended as shown in Appendix A

MOTION: To approve the coding and guideline note changes as amended. CARRIES 5-0.

- **Topic: Preventive services guideline edits**

Discussion: Livingston introduced the summary document. There was no discussion.

Recommended Actions:

1) Amend Guideline Note 106 as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 5-0.

- **Topic: Bariatric Surgery Guideline**

Discussion: Smits reviewed the summary document. Public testimony was heard from Jennifer Valley, a cannabis grower and breeder. Ms. Valley testified about her own experience with the benefits of cannabis oil for treatment of cancer. She notes that

research into the impacts of cannabis are limited by federal rules. She testified that cannabis oil helps lower opioid use. She would like cannabis oil covered for pain, diabetes, cancer, and seizures for OHP patients. She would also like studies done on outcomes of medical marijuana.

Livingston pointed the VbBS members to the Institute of Medicine study on medical marijuana. Staff noted that there is an issue with using Medicaid money to pay for marijuana; such payment is not allowed since marijuana is federally still classified as a Schedule 1 controlled substance.

There was minimal discussion about the staff recommendations to not change the bariatric surgery guideline regarding marijuana use. Abuse of and dependence on marijuana will still be a contraindication to surgery, but not casual use.

Recommended Actions:

1) No changes were made to Guideline Note 8 BARIATRIC SURGERY

MOTION: To make no changes to Guideline Note 8. CARRIES 5-0.

- **Public Comment:**

  No additional public comment was received

- **Issues for next meeting:**

  None carried forward from this meeting

- **Next meeting:**

  March 9, 2017 at Clackamas Community College, Wilsonville Training Center, Wilsonville, Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 12:15 PM.

Appendix A
Revised Guideline Notes

GUIDELINE NOTE 34, ~~ORAL SURGERY~~ EXTRACTION OF IMPACTED WISDOM TEETH

Line 349

~~Treatment only for symptomatic dental pain, infection, bleeding or swelling (D7220, D7230, D7240, D7241, D7250).~~

Extraction of impacted wisdom teeth (D7220, D7230, D7240, D7241, D7250) is only included on this line when there is

1) evidence of pathology. Such pathology includes unrestorable caries, non-treatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumor, tooth/teeth impeding surgery or reconstructive jaw surgery, and when a tooth is involved in or within the field of tumor resection OR
2) two or more episodes of pericoronitis OR
3) severe pain directly related to the impacted tooth that does not respond to conservative treatment
    a. extraction for pain or discomfort related to normal tooth eruption or for non-specific symptoms such as "headaches" or "jaw pain" is not considered medically or dentally necessary for treatment.

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 316,450,479

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 316 or line 450 for children up through and including age 7. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 479.

For coverage to be considered on either Line 316, Line 450 or Line 479, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay ~~(~~should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Appendix A
Revised Guideline Notes

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older ~~over 3 years~~ who are having their second set of tubes.

GUIDELINE NOTE 98, SIGNIFICANT INJURIES TO LIGAMENTS AND TENDONS AND MENISCI

Lines 381,436,611

Significant injuries to ligaments and/or tendons and/or menisci are those that result in clinically demonstrable joint instability or mechanical interference with motion. Significant injuries are covered on Line 381 or Line 436; non-significant injuries are included on Line 611.

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3

Included on this line are the following preventive services: ~~as required by federal law:~~

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016:
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   a. USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines:
   As retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

~~USPSTF "D" recommendations are included on line 625, PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS.~~

Appendix B
New Guideline Notes

GUIDELINE XXX, FECAL MICROBIOTA TRANSPLANT

Line 150

Fecal microbiota transplant (FMT; CPT 44705, HCPCS G0455) is included on this line for treatment of recurrent C difficile infection only.

GUIDELINE NOTE XXX, CHOLECYSTITIS

Lines 59, 645

Cholecystitis is defined as the presence of right upper quadrant abdominal pain, mass, tenderness or a positive Murphy's sign, AND

1) Evidence of inflammation (for example: fever, elevated white blood cell count, elevated C reactive protein), OR
2) Ultrasound findings characteristic of acute cholecystitis (for example: gallbladder wall thickening) or non-visualization of the gall bladder on oral cholecystegram or HIDA scan, or gallbladder ejection fraction of < 35%

ICD-10 K82.8 (Other specified diseases of gallbladder) is included on line 59 when the patient has

1) Porcelain gallbladder, or
2) Gallbladder dyskinesia with a gallbladder ejection fraction <35%.

Otherwise, K82.8 is included on line 645.

Section 2.0

Staff Report

Errata
March 2017

1) GN 49 contains a HCPCS code which is not related to external cardiac defibrillators and does not appear on any line listed. This code was removed.

GUIDELINE NOTE 49, WEARABLE CARDIAC DEFIBRILLATORS

Lines 73,103,115,193,286,352

Wearable cardiac defibrillators (WCDs; CPT 93745, HCPCS ~~E0617,~~ K0606-K0609) are included on these lines for patients at high risk for sudden cardiac death who meet the medical necessity criteria for an implantable cardioverter defibrillator (ICD) as defined by the CMS 2005 National Coverage Determination but are unable to have an ICD implanted due to medical condition (e.g. ICD explanted due to infection with waiting period before ICD reinsertion or current medical condition contraindicates surgery). WCDs are not included on these lines for use during the waiting period for ICD implantation after myocardial infarction, coronary bypass surgery, or coronary artery stenting.

2) GN42 had an incorrect number of days published. The VBBS agreed upon number of headache days per month was 7; 6 was incorrectly included in the published guideline note.

GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE

Line 415

Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant)
C) treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least ~~6~~ 7 headache days per month compared to baseline headache frequency.

3. The ICD-9 diagnosis code for rectal abscess (566) was on the equivalent of line 210 SUPERFICIAL ABSCESSES AND CELLULITIS with all the appropriate CPT codes for treatment. The ICD-10 code for rectal abscess (K61.1) and similar diagnoses were placed on line 51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS while the appropriate CPT codes for treatment were left on line 210.

1) ICD-10 diagnoses codes for rectal and anal abscesses were removed from line 51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS and added to line 210 SUPERFICIAL ABSCESSES AND CELLULITIS to pair with appropriate treatment codes
    a. K61.0 Anal abscess
    b. K61.1 Rectal abscess
    c. K61.2 Anorectal abscess
    d. K61.3 Ischiorectal abscess
    e. K61.4 Intrasphincteric abscess

4. The CPT codes for various nerve blocks were removed from approximately 360 lines on the Prioritized List as an errata in February, 2016, and recommended placement on the Ancillary File. However, these codes were never added to the Ancillary Guideline A1 regarding nerve blocks. These codes are now being added to the guideline.

ANCILLARY GUIDELINE A1, NERVE BLOCKS

The Health Evidence Review Commission intends that single injection and continuous nerve blocks (CPT 64400-64450, 64461-64463, 64505-64530) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks, are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—March, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
P29.0	Neonatal cardiac failure	2 BIRTH OF INFANT 102 HEART FAILURE	HSD requested that P29.0 pair with ECMO CPT codes. P29.0 is more appropriately on line 102 which has ECMO codes, as well as NICU codes.	Add P29.0 to line 102 Remove P29.0 from line 2
33475	Replacement, pulmonary valve	74 CONGENITAL PULMONARY VALVE ANOMALIES	HSD requested that 33475 pair with Q22.2 (Congenital pulmonary valve insufficiency). 33475 is on lines 73,86,115,190,193,262,290.	Add 33475 to line 74
00102	Anesthesia for procedures involving plastic repair of cleft lip	305 CLEFT PALATE AND/OR CLEFT LIP	HSD requested that 00102 be removed from the Services Recommended for Non-Coverage Table (SRNC). The procedures associated with this anesthesia (CPT 40700 Plastic repair of cleft lip/nasal deformity and similar) are on line 305. Anesthesia codes are generally ancillary; however, this code is only used with procedure codes on line 305	Add 00102 to line 305
S0265	Genetic counseling, under physician supervision, each 15 minutes		HSD requested that S0265 be added to the Diagnostic Procedures File and removed from SRNC. CPT 96040 (Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family) is diagnostic.	Remove S0265 from the Services Recommended for Non-Coverage Table Advise HSD to add S0265 to the Diagnostic Procedures File

Consent Agenda Issues—March, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
87338	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Helicobacter pylori, stool		HSD requested that 87338 be removed from line 60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE and made diagnostic. Similar testing for H Pylori is diagnostic.	Remove 87338 from line 60 Advise HSD to add 87338 to the Diagnostic Workup File
92002-92014	Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program	212 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	HSD requested that ophthalmology visits be paired with S01.112A (Laceration without foreign body of left eyelid and periocular area). The Ophthalmology code series are on many lines.	Ass 92002-92014 to line 212
12011-12018	Repair of wound of the face, ears, eyelids, nose, lips, and/or mucous membrane	233 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	HSD requested that 12011 pair with S02.2XXB (Fracture of nasal bones, initial encounter for open fracture). 12011 is on lines 136,212,234,280,359,390,626,638	Add 12011-12018 to line 233
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan	160 ACROMEGALY AND GIGANTISM	Line 160 does not have any radiation therapy CPT codes and therefore does not need 77338.	Remove 77338 from line 160

Consent Agenda Issues—March, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
H0048	Alcohol and/or other drug testing: collection and handling only, specimens other than blood	4 SUBSTANCE USE DISORDER 66 SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS 69 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL 614 ABUSE OF NONADDICTIVE SUBSTANCES	H0048 is currently on lines 4,66,69,614 (drug and alcohol lines). This type of testing may be used for UDS for opioid prescriptions or other administrative purposes.	Remove H0048 from lines 4, 66, 59 and 614 Advise HSD to add H0048 to the Diagnostic Procedures File
T1016	Case management, each 15 minutes	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	HSD is finding many requests for pairing T1016 with diagnoses on line 3. Case managers are likely trying to assist patients in getting appropriate screening tests. T1016 is on approximately 40 lines.	Add T1016 to line 3
R13.2	Oral dysphagia	350 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS	Dr. Joyce Liu from Kaiser requested that speech therapy CPT codes (92507 and 92508) be paired with R13.12. 92507 and 92508 on are 17 lines, including 350	Add R13.2 to line 350
Z72.0	Tobacco use	5 TOBACCO DEPENDENCE	HSD requested review of Z72.0. Z72.0 is currently informational. Can be used to pair with tobacco counseling. Add to line 5.	Add Z72.0 to line 5

Consent Agenda Issues—March, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
92526	Treatment of swallowing dysfunction and/or oral function for feeding	19 FEEDING PROBLEMS IN NEWBORNS 153 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD 599 TONGUE TIE AND OTHER ANOMALIES OF TONGUE	Kaiser has requested that 92526 pair with various feeding diagnoses for newborns found on line 19. They also requested that 92526 pair with F50.89 (Other specified eating disorder—includes avoidant/restrictive food intake disorder) which is on line 153. Lastly, they requested pairing with diagnoses on line 599. Currently, 92526 is on 12 lines.	Add 92526 to lines 19, 153, and 599
30020	Drainage abscess or hematoma, nasal septum	210 SUPERFICIAL ABSCESSES AND CELLULITIS	HSD has requested that 30020 pair with J34.0 (Abscess, furuncle and carbuncle of nose). 30020 is currently on lines 469 and 509.	Add 30020 to line 210
31645	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with therapeutic aspiration of tracheobronchial tree, initial (eg, drainage of lung abscess)	428 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	HSD requested that 31645 pair with J95.00 (Unspecified tracheostomy complication). 31645 is currently on lines 51,62,209,238,267,468. Similar bronchoscopy codes appear on line 428.	Add 31645 to line 428

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
J98.09	Other diseases of bronchus, not elsewhere classified	62 BRONCHIECTASIS	HSD requested that 31645 pair with J98.09. J98.09 currently only appears on the cleft palate line. This code can be used for stenosis of bronchus, ulcer of bronchus, and other non-cleft palate related conditions. Line 62 contains bronchiectasis diagnoses which are clinically similar to stenosis of bronchus. Line 62 contains 31645.	Add J98.90 to line 62
43300-43312	Esophagoplasty (plastic repair or reconstruction), cervical or thoracic approach; with or without repair of tracheoesophageal fistula	231 RUPTURED VISCUS	HSD requested that 43310 pair with K22.3 (Perforation of esophagus) which is on line 231. Similar codes include 44300-43312. 43300-43312 are currently only on line 68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE.	Add 43310-43312 to line 231
43241	Esophagogastroduodenoscopy, flexible, transoral; with insertion of intraluminal tube or catheter	46 INTUSSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, HAZARDOUS FOREIGN BODY IN GI TRACT WITH RISK OF PERFORATION OR OBSTRUCTION	HSD requested that 43241 pair with K56.69 (Other intestinal obstruction) which includes small intestinal obstruction. 43241 is currently on lines 60,107.	Add 43241 to line 46

Minor Newborn Conditions

Question: How should normal newborn care procedure codes be paired with certain diagnosis codes that can represent both major and minor conditions?

Question source: HSD

Issue: HSD has seen multiple requests for pairing CPT codes for care of normal newborns with newborn condition ICD-10 codes that are on specific lines for that condition. These specialized lines contain only inpatient/NICU care CPT codes, not normal newborn care CPT codes. Most of these ICD-10 codes have subdiagnoses that can represent major illness or very minor conditions. The normal newborn CPT codes currently do not appear on any of these specialized lines.

The CPT codes in question currently only appear on line 2 BIRTH OF INFANT and line 19 FEEDING PROBLEMS IN NEWBORNS:

99460 Initial hospital or birthing center care, per day, for evaluation and management of normal newborn infant

99462 Subsequent hospital care, per day, for evaluation and management of normal newborn

99463 Initial hospital or birthing center care, per day, for evaluation and management of normal newborn infant admitted and discharged on the same date

Also in this series but not requested for pairing: **99461** Initial care, per day, for evaluation and management of normal newborn infant seen in other than hospital or birthing center

On review, HERC staff recommends that these codes be paired. Pairing could be accomplished by either adding the ICD-10 codes shown in the table below to line 2 BIRTH OF INFANT or by adding the normal newborn CPT codes to the specialized lines containing these diagnoses. There are more newborn lines that contain possibly minor conditions than those identified in claims reviewed by HSD.

ICD-10 Code	Code description	Subdiagnoses	Current line(s)
P22.1	Transient tachypnea of newborn		11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
P28.3	Primary sleep apnea of newborn		11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
P28.89 P28.9	Other specified respiratory conditions of newborn Respiratory condition of newborn, unspecified	Congenital laryngeal stridor Sniffles in newborn Snuffles in newborn	11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
P59.0	Neonatal jaundice associated with preterm delivery		106 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE
P59.9	Neonatal jaundice, unspecified	Can be major jaundice or physiologic jaundice	106 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE
P61.0	Transient neonatal thrombocytopenia		36 HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN
P70.4	Other neonatal hypoglycemia	Transitory neonatal hypoglycemia (may be minor or serious)	21 SYNDROME OF "INFANT OF A DIABETIC MOTHER" AND NEONATAL HYPOGLYCEMIA
P81.8	Other specified disturbances of temperature regulation of newborn		146 CONDITIONS INVOLVING THE TEMPERATURE REGULATION OF NEWBORNS
P96.1	Neonatal withdrawal symptoms from maternal use of drugs of addiction		31 DRUG WITHDRAWAL SYNDROME IN NEWBORN

HERC staff recommendations:

1) Add ICD-10 P22.1 (Transient tachypnea of newborn) to line 2 BIRTH OF INFANT and remove from line 11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
    a. By definition a normal condition
2) Add 99460-99463 (Initial and subsequent hospital care for normal newborns) to all newborn lines with possible minor conditions:
    a. 11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
    b. 21 SYNDROME OF "INFANT OF A DIABETIC MOTHER" AND NEONATAL HYPOGLYCEMIA
    c. 22 OMPHALITIS OF THE NEWBORN AND NEONATAL INFECTIVE MASTITIS
    d. 27 INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN
    e. 31 DRUG WITHDRAWAL SYNDROME IN NEWBORN
    f. 36 HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN
    g. 45 HYPOCALCEMIA, HYPOMAGNESEMIA AND OTHER ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN
    h. 106 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE
    i. 149 ANEMIA OF PREMATURITY OR TRANSIENT NEONATAL NEUTROPENIA
    j. 296 ADRENAL OR CUTANEOUS HEMORRHAGE OF FETUS OR NEONATE
    k. 648 EDEMA AND OTHER CONDITIONS INVOLVING THE SKIN OF THE FETUS AND NEWBORN

Screening Colonoscopy

Issue: Screening colonoscopy is a USPSTF level A recommendation for people over age 50 as an option for screening for colon cancer. The ICD-10 code Z12.11 (Encounter for screening for malignant neoplasm of colon) is on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS. However, none of the colonoscopy codes are on this line. If no polyps are found, then CPT 45378 is likely to be used; however, this code is most appropriately diagnostic as it might be used for non-colon cancer screening purposes (i.e. investigation of diarrhea or rectal bleeding). If a polyp is found during a screening colonoscopy, then CPT 45384 or 45385 are likely to be used; these codes appear on several lines but not line 3. Current ACA rules agree with coverage of colonoscopy with polyp removal as part of the colon cancer screening coverage. The OHP medical directors all agree with this change.

HERC staff recommendation:

1) Add CPT 43584 and 45385 to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

CPT	Code Descriptions	Current Placement
45378	Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed	Diagnostic Procedures File
45379	Colonoscopy, flexible; with removal of foreign body(s)	46,523
45380	Colonoscopy, flexible; with biopsy, single or multiple	Diagnostic Procedures File
45381	Colonoscopy, flexible; with directed submucosal injection(s), any substance	32,46,60,105,161,170,189, 478,624, 642
45382	Colonoscopy, flexible; with control of bleeding, any method	32,60,105,161,170,189,231 ,345, 478,624,642
45384	**Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps**	46,60,105,161,170,642
45385	**Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique**	46,105,161,170,642
45386	Colonoscopy, flexible; with transendoscopic balloon dilation	32,46,105,161,642
45388	Colonoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	46,60,105,161,170,642
45389	Colonoscopy, flexible; with endoscopic stent placement (includes pre- and post-dilation and guide wire passage, when performed)	32,46,105,161,642
45390	Colonoscopy, flexible; with endoscopic mucosal resection	Diagnostic Procedures File
45391	Colonoscopy, flexible; with endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures	Services Recommended for Non-coverage File
45392	Colonoscopy, flexible; with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s), includes endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures	Services Recommended for Non-coverage File
45393	Colonoscopy, flexible; with decompression (for pathologic distention) (eg, volvulus, megacolon), including placement of decompression tube, when performed	46,105

Straightforward Coding Changes
Injuries to Major Blood Vessels

Issue: At the February, 2017 VBBS meeting, two major blood vessel injury lines were merged (line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES and 281 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY) and major blood vessel injury ICD-10 and repair CPT codes were removed from line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME. It was noted that several codes involving minor blood vessels (i.e. vessels of fingers or toes) were added to new line 82 INJURY TO MAJOR BLOOD VESSELS and VbBS requested that HERC staff review these codes and suggest their movement to a lower line.

HERC staff recommendations:

1) Remove CPT 35207 (Repair blood vessel, direct; hand, finger) from line 82 INJURY TO MAJOR BLOOD VESSELS
    a. Already appears on line 294 CRUSH AND OTHER INJURIES OF DIGITS
2) Remove ICD-10 S27.9XXA, S27.9XXD (Injury of unspecified intrathoracic organ) from line 82 and add to line 84 INJURY TO INTERNAL ORGANS
    a. Added by mistake to new line
3) Remove ICD-10 S45.301A, S45.301D, S45.302A, S45.302D, S45.309A, S45.309D, S45.311A, S45.311D, S45.312A, S45.312D, S45.319A, S45.319D, S45.391A, S45.391D, S45.392A, S45.392D, S45.399A, S45.399D (injury of superficial vein at shoulder and upper arm level) from line 82 and add to line 212 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
    a. Matches placement of other superficial vessels

Blood Lead Level Screening

Question: Should coverage of blood lead level screening be clarified on the Prioritized List?

Question source: Kim Wentz

Issue: There is some confusion in the community about lead screening, whether for OHP children this involves screening questionnaires or blood lead level screening.

Guideline Note 106 currently requires coverage of Bright Futures Guidelines. The Bright Futures Periodicity Schedule says lead screening should be performed at 12 and 24 months with a footnote "Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas." Additional risk assessments are to be performed at additional ages.

Many providers of pediatric care are aware of "targeted approaches" and think risk-based screening alone is sufficient.

The rate of blood lead level screening is very low in Oregon, approximately 10% according to public health.

CMS issued a 2016 Bulletin clarifying required coverage. CMS requires blood lead screening tests at ages 12 months and 24 months. In addition, any child between ages 24 and 72 months with no record of a previous blood lead screening test must receive one.

Clarity on the definition and periodicity of lead screening would be helpful.

Prioritized List Status

Code	Code Description	Placement
83655	Lead	Diagnostic Procedures File

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3

Included on this line are the following preventive services:

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016:
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   a. USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List

2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines:
   As retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

HERC Staff Recommendations:
Modify Guideline Note 106 as follows:

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3

Included on this line are the following preventive services:

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016:
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   a. USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
   a. Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines:
   As retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop S2-26-12
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CENTERS FOR MEDICARE & MEDICAID SERVICES
CENTER FOR MEDICAID & CHIP SERVICES

CMCS Informational Bulletin

DATE: November 30, 2016

FROM: Vikki Wachino, Director
Center for Medicaid and CHIP Services

SUBJECT: **Coverage of Blood Lead Testing for Children Enrolled in Medicaid and the Children's Health Insurance Program**

Background

The recent water crisis in Flint, Michigan, serves as a reminder of the importance of blood lead screening for children. While substantial environmental improvements have been made to reduce exposure to lead, over four million children are estimated to reside in housing where they are exposed to lead.[1] The Centers for Disease Control and Prevention (CDC) projects that there are about half a million children between the ages of one and five years in the United States who possess blood lead levels greater than 5 micrograms per deciliter (µg/dL), which is the threshold level at which CDC recommends public health actions are taken.[2] It is essential that children enrolled in the Medicaid and Children's Health Insurance Program (CHIP) receive blood lead screening tests as required in order to identify children with elevated blood lead levels (EBLLs) at as young an age as possible. The goal of lead screening is to assist children before they are harmed. Comprehensive screening and surveillance ensures that lead-poisoned infants and children receive medical and environmental follow-up as soon as possible and allows for the development of neighborhood-based efforts to prevent lead poisoning.[3] Lead exposure can impact nearly every system in the body and often goes undetected because at low levels of exposure, it can occur without any obvious symptoms.[4] Exposure to lead can cause damage to the brain and nervous system, slowed growth and development, learning and behavior problems, and hearing and speech problems. While lead paint has historically been the greatest source of exposure to lead, children can be exposed to lead from additional sources (such as lead smelters, leaded pipes, solder and plumbing fixtures, and consumer products) and through different pathways (such as air, food, water, dust and soil).[5]

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[1] Lead. (2016, January 29). Retrieved from http://www.cdc.gov/nceh/lead/
[2] Lead. (2016, January 29). Retrieved from http://www.cdc.gov/nceh.lead. In 2012, the reference level to identify children with blood lead levels that are much higher than most children's levels was changed to 5 µg/dL.
[33] Lead – CDC's Childhood Lead Poisoning Prevention Program. (2015, February 9). Retrieved from http://www.cdc.gov/nceh/lead/about/program.htm
[4] Lead. (2016, January 29). Retrieved from http://www.cdc.gov/nceh/lead/
[5] Lead (2015, May 29). Retrieved from http://www.cdc.gov/nceh/lead/tips/sources.htm

Ensuring that all children enrolled in Medicaid and CHIP receive blood lead screening tests as required involves a commitment and action by state Medicaid and CHIP agencies as well as partnerships between these state agencies, health care providers and other state agencies, such as health departments and lead poisoning prevention programs. This Informational Bulletin provides an overview of the screening requirements for children enrolled in Medicaid and CHIP and also identifies steps that states can take to improve lead screening efforts in order to reach children at risk of EBLLs.

Coverage of Lead Screening

Medicaid

All children enrolled in Medicaid, regardless of whether coverage is funded through title XIX or XXI, are required to receive blood lead screening tests at ages 12 months and 24 months. In addition, any child between ages 24 and 72 months with no record of a previous blood lead screening test must receive one.[6] Completion of a risk assessment questionnaire does not meet the Medicaid requirement. The Medicaid requirement is met only when the two blood lead screening tests identified above (or a catch-up blood lead screening test) are conducted.

Under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit, Medicaid provides comprehensive coverage, for any service described in section 1905(a) of the Social Security Act needed that is medically necessary to correct or ameliorate defects in physical and mental illnesses or conditions identified by the screening services, whether or not such service is otherwise covered under the state plan. Medicaid also provides reimbursement for lead investigations in the home or primary residence of a child with an EBLL. Any lead investigation must be conducted by a credentialed health practitioner who meets the qualifications established by the state and is undertaken to identify the source of lead exposure.[7] States have an affirmative obligation to ensure that Medicaid-eligible children and their families are aware of the services that are a part of the EPSDT benefit and have access to required screenings and necessary treatment services.[8]

It is not necessary to refer a child to a separate laboratory facility for a blood lead screening test, Medicaid will pay for a blood sample drawn in the physician's office using a point of service blood lead screening test. However, there is concern that not all blood lead screening tests conducted in provider's offices are coded in a way to be included in Medicaid screening data. States should provide clear guidance to providers on these data and reporting requirements to ensure that results are coded correctly and reported to state health departments for inclusion in state lead screening surveillance data.

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[6] Medicaid Manual section 5123.2.D.1.

[7] Medicaid Manual section 5123.2.D.1.a

[8] Section 1902(a)(43)(A) of the Social Security Act (the Act) and Medicaid Manual section 5010

[8] http://www.cdc.gov/nceh/lead/policy"

In 2012, the Centers for Medicare & Medicaid Services (CMS) expanded its lead screening policy to allow states to request approval from CMS to implement a targeted lead screening program.[9] This change was made to align the Medicaid lead screening policy with that of the CDC, recognizing that risk of exposure to lead in some states may not be evenly spread throughout the state, and to allow states' resources to be used more efficiently for children most at risk.

States that wish to implement a targeted lead screening plan need to work closely with their state health departments to determine an appropriate targeting methodology for the state. State proposals need to include information such as the areas of local risk for elevated blood lead levels, information on current estimates of blood lead screening rates by local jurisdiction and risk status, and a proposed blood lead screening strategy that will focus available resources on the population at highest risk. CMS provided detailed guidance on how states can develop and submit proposals through two CMCS Informational Bulletins (CIBs) issued on March 30, 2012, and June 22, 2012. Both of these CIBs, as well as a *Guide For States Interested in Transitioning to Targeted Blood Lead Screening for Medicaid-Eligible Children,* are available on Medicaid.gov.[10] All submitted proposals are jointly reviewed by CMS and CDC. To date, Arizona is the only state that has an approved targeted lead screening policy.

CHIP

Separate CHIP programs do not have the same requirements for universal lead screening as Medicaid, although we encourage states to align their CHIP and Medicaid screening policies. States are required to offer well-child visits,[11] and must select a periodicity schedule. States commonly use the Bright Futures periodicity schedule (developed by the American Academy of Pediatrics), which recommends blood lead screening tests at 12 months and 24 months for children at risk of lead exposure or in high prevalence areas.[12] States that offer EPSDT benefits through their separate CHIP should follow Medicaid's universal screening policy.

[9] The March 30, 2012, and June 22, 2012, CIBs are available on Medicaid.gov through these links: http://www.medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-03-30-12.pdf and http://www.medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-06-22-12.pdf. The guidance document is available at https://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/downloads/targetedleadscreening.pdf.

[10] The March 30, 2012, and June 22, 2012, CIBs are available on Medicaid.gov through these links: http://www.medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-03-30-12.pdf and http://www.medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-06-22-12.pdf. The guidance document is available at https://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/downloads/targetedleadscreening.pdf.

[11] 42 CFR 457.10(b)

[12] Bright Futures/American Academy of Pediatrics. Updated 10/2015. Recommendations for Preventive Pediatric Health Care - footnotes 19 and 20.

Data and Data Reporting to CMS

Medicaid agencies are required to submit EPSDT data annually using the Form CMS-416[13], including the number of blood lead screening tests for children enrolled in Medicaid, from birth to age 6, regardless of whether they are funded through title XIX or XXI. According to data reported on Form CMS-416, the number of children enrolled in Medicaid who receive blood lead screening tests varies considerably from state to state. When the number of blood lead screening tests reported for 2015 on the Form CMS-416 are compared to the number of children that are eligible for EPSDT and continuously enrolled in Medicaid for at least 90 days, the data suggests that only about 38 percent of children ages 1 – 2 are reported to have been screened. CMS believes that this underrepresents the actual number of children who received blood lead screening tests because the CMS-416 captures claims and encounter based data; the form does not capture screenings that are not paid for by Medicaid, such as screenings performed by clinics using CDC funding or funded by state health departments. However, the data does indicate that there are many children at risk of lead exposure that are not being tested.

The instructions for the Form CMS-416 require states to report data that includes services reimbursed directly by the state – this requirement applies regardless of whether the reimbursement happens under fee-for-service, or through managed care, prospective payment, or other payment arrangement or through any other health plans that contract with the state. States are required to collect encounter data (or other data as necessary) from managed care and prospective payment entities in sufficient detail to provide the information required by the report.[14]

Specific to the blood lead screening line (line 14) on the Form CMS-416, states may use one of two methods, or a combination of these methods, to calculate the number of blood lead screening tests provided:

1. Count the number of times Current Procedural Terminology (CPT) code 83655 (“lead”) for a blood lead screening test is reported within certain ICD-10-CM codes; or
2. Include data collected from use of the Healthcare Effectiveness Data and Information Set (HEDIS) blood lead screening measure developed by the National Committee for Quality Assurance (NCQA) to report blood lead screening tests, if your state has elected to use this performance measure.[15]

It is essential that the data submitted using the Form CMS-416 is accurate, and we request that states review their data carefully prior to submission. As CMS and states begin to use the Transformed Medicaid Statistical Information System (T-MSIS), we expect that CMS will be

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[13] The CMS-416 form and instructions can be accessed through the EPSDT page on Medicaid.gov: https://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Early-and-Periodic-Screening-Diagnostic-and-Treatment.html. State reported data is also available through this link.

[14] Instructions for Completing Form CMS-416: Annual Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) Participation Report. Version 3, as of November 17, 2014; page 1. https://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/downloads/cms-416-instructions.pdf

[15] Instructions for Completing Form CMS-416; Version 3; page 11.

able gather more timely and accurate estimates of blood lead screening rates than what is currently indicated by the Form CMS-416.

As referenced above, NCQA has a HEDIS quality measure for blood lead testing of 2-year-old children continuously enrolled in Medicaid for eleven months. NCQA has reported, on average, a blood lead screening rate of 66 percent for Medicaid managed care plans that reported on this measure over the last 2 years. Using and reporting on this measure is optional, with approximately 30 states reporting, so it is not representative of the entire country.[16] However, it does provide another data source and an opportunity to evaluate Medicaid managed care plans that report on this measure. Data from this measure can be used for annual Form CMS-416 reporting.

State Action

There are a number of actions that we encourage states to undertake in order to improve blood lead screening rates and reporting:

- Review your state's most recent Form CMS-416 data submission and any other available data sources (including CDC surveillance data) to understand your state's blood lead screening rate and to determine areas for improvement of data submission and to identify inconsistencies in rates of blood lead screening tests, as well as any data reporting errors that might exist. If an error in reporting on the Form CMS-416 is identified, corrected data should be submitted to CMS. When reviewing your state's data submitted on the Form CMS-416, please ensure that the data submitted includes all delivery systems, as specified in the CMS-416 instructions.

- Review all coverage materials, manuals, periodicity schedules, and your state's website to ensure that information on lead screening is clearly written and consistent with Medicaid and CHIP requirements. Also review information on lead screening distributed by your Department of Health, and ensure that there is consistent messaging across state agencies. Documents that should be reviewed include provider materials/manuals, managed care contracts, and educational materials for beneficiaries and their families. Consider sharing sample materials with a group of Medicaid and CHIP providers and beneficiaries prior to release to ensure that the messaging is clear and understandable.

- Collaborate with your state's health department and lead poisoning and prevention program to reach children who have not received required blood lead screening tests. Collaboration could include combined outreach to families and data sharing agreements between agencies.

[16] Lead Screening in Children. NCQA. http://www.ncqa.org/report-cards/health-plans/state-of-health-care-quality/2015-table-of-contents/lead-screening

- Partner with providers, such as pediatricians, family physicians, and other experts in pediatric health care to ensure that children enrolled in Medicaid or CHIP receive required blood lead screening tests. Provide clear information on the Medicaid and CHIP lead screening requirements to providers; ensure that they understand these requirements; and request that any materials prepared by the provider also include clear language and guidance to patients. We encourage states to align their CHIP and Medicaid screening policies.

- Require managed care plans to engage in your efforts to improve blood lead screening rates. With over two-thirds of children enrolled in Medicaid and CHIP covered under managed care, managed care plans have an important role to play in improving lead screening. States are encouraged to consider using the following managed care tools to effectively partner with managed care plans to improve blood lead screening tests:
    - Contracts: Include lead screening requirements in managed care contracts in order to emphasize its importance and ensure that additional monitoring occurs through the annual state report required by 42 CFR 438.66.
    - Data Reporting and Quality Measures: As mentioned above, the HEDIS Medicaid–only lead screening quality measure assesses the percentage of children enrolled in Medicaid for 11 continuous months with one or more blood tests for lead poisoning by their second birthday. CMS encourages states to require managed care plans participating in their state Medicaid programs to use this important plan-level quality measure. While the HEDIS measure is Medicaid-specific, CHIP agencies could consider a HEDIS-like measure to monitor screening of children enrolled in CHIP managed care.
    - Performance Improvement: Using HEDIS or other performance information, states should compare plan level performance and consider requiring managed care plans to implement performance improvement projects (PIPs) focusing on blood lead screenings. In addition, managed care plans can provide incentives related to increased screening rates.
    - Quality Assessment and Performance Improvement Programs (QAPI) Managed Care Quality Strategy: Include screening improvements as one of the quality metrics required by the state for manage care plans under QAPI (42 CFR 438.330(c) and 457.1240(b)) and reflect this requirement in the state managed care quality strategy required by 42 CFR 438.340 and 457.1240(e).

- Consider developing a state-designed Health Services Initiative (HSI) to increase blood lead screening rates for young children. HSIs are available under title XXI to improve the health of low-income children,[17] including children enrolled in Medicaid and CHIP, and can include both direct services and public health initiatives. Claims for HSIs and administrative expenses cannot exceed 10 percent of the total amount of title XXI funds

[17] HSIs are permitted under section 2105(a)(1)(D)(ii) of the Act and are defined in the regulations at 42 CFR 457.10

claimed by the state each quarter.[18] Within the 10 percent limit, states must fund costs associated with administration of the CHIP state plan first; any funds left over may be used for an HSI.

- Missouri currently has an approved HSI to improve lead screening rates. Through a Memorandum of Agreement with the Missouri Department of Health & Senior Services, the State provides funding annually for local public health departments to provide blood lead screenings tests as well as outreach and education to children in areas that are designated as warranting higher vigilance in testing children for elevated blood lead levels. The state follows the EPSDT guidelines for testing. In addition, Missouri has a managed care incentive for lead screening.

- Leverage partnerships with nontraditional providers within your network. For example, Women, Infant and Children (WIC) clinics, local health clinics, Federally Qualified Health Centers, and school-based health centers provide blood lead screening tests within the scope of their services. If you already recognize these clinics as providers, encourage these providers to administer blood lead screening tests while Medicaid and CHIP children are visiting these clinics for other services. This reduces the number of missed opportunities for a child to receive a required blood lead screening test and allows your state to capture lead screening data, as it will be included in your claims/encounter data. In addition, consider partnering with your state's child care licensing entity to distribute information about blood lead screening tests.

As lead abatement plays a significant role in reducing lead exposure for children, collaboration with state housing departments is also recommended. It is important to note that accurate state data on the prevalence of elevated blood lead levels is necessary to apply to lead abatement grant programs.

It is expected that as the blood lead screening rates for children enrolled in Medicaid and CHIP increase, the number of children who are identified as having EBLLs will also increase. States need to think beyond screening, and ensure that guidance and resources are available and in place to support providers, families and other stakeholders who work to obtain appropriate services for children with EBLLs. In addition, improved blood lead screening data will assist cities and states as they apply for grant funding related to primary prevention of lead exposure, such as grants from the Department of Housing and Urban Development.

As stated earlier, the EPSDT benefit includes coverage of any medically necessary medical service to correct or ameliorate defects and physical and mental illnesses and conditions discovered by screening services. In addition, case management can be used to provide services

[18] Per section 2105(a)(1)(D), HSI expenditures (including administration of the HSI itself) are subject to a cap that also applies to administrative expenses. Under section 2105(c)(2)(A) of the Act, claims for HSIs and administrative expenses cannot exceed 10 percent of the total amount of title XXI funds claimed by the state each quarter.

to children with EBLLs.[19] Case management benefits include services that assist eligible individuals gain access to needed medical, social, educational, and other services. They must include all of the following: comprehensive assessment of an eligible individual; development of a specific care plan; referral to needed services; and monitoring activities. Under this benefit, states may target case management services to a specific group of individuals or to individuals who reside in specified areas of the state (or both).

CMS is committed to working with states to improve blood lead screening rates for children enrolled in Medicaid and CHIP, and is available to provide technical assistance. For further information, please contact Karen Matsuoka, PhD, CMCS Chief Quality Officer and Director, Division of Quality and Health Outcomes, at karen.matsuoka@cms.hhs.gov or 410-786-9726.

[19] Case management services are defined at 42 CFR 440.169 and 42 CFR 441.18.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Recommendations for Preventive Pediatric Health Care

Bright Futures/American Academy of Pediatrics

Bright Futures
prevention and health promotion for infants, children, adolescents, and their families™

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. Additional visits may become necessary if circumstances suggest variations from normal.

Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits.

These guidelines represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

Refer to the specific guidance by age as listed in *Bright Futures* guidelines (Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures Guidelines for Health Supervision of Infants, Children and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008).

The recommendations in this statement do not indicate an exclusive course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

	INFANCY								EARLY CHILDHOOD							MIDDLE CHILDHOOD						ADOLESCENCE										
AGE[1]	**Prenatal**[2]	**Newborn**[3]	**3-5 d**[4]	**By 1 mo**	**2 mo**	**4 mo**	**6 mo**	**9 mo**	**12 mo**	**15 mo**	**18 mo**	**24 mo**	**30 mo**	**3 y**	**4 y**	**5 y**	**6 y**	**7 y**	**8 y**	**9 y**	**10 y**	**11 y**	**12 y**	**13 y**	**14 y**	**15 y**	**16 y**	**17 y**	**18 y**	**19 y**	**20 y**	**21 y**
HISTORY Initial/Interval	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
MEASUREMENTS																															
Length/Height and Weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Head Circumference		●	●	●	●	●	●	●	●	●	●	●																			
Weight for Length		●	●	●	●	●	●	●	●	●	●																				
Body Mass Index[5]												●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood Pressure[6]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SENSORY SCREENING																															
Vision[7]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	★	●	★	●	★	●	★	★	●	★	★	★	★	★
Hearing		●[8]	★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	★	●	★	●	★	★	★	★	★	★	★	★	★	★	★
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT																															
Developmental Screening[9]								●			●		●																		
Autism Screening[10]											●	●																			
Developmental Surveillance		●	●	●	●	●	●		●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Psychosocial/Behavioral Assessment		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alcohol and Drug Use Assessment[11]																					★	★	★	★	★	★	★	★	★	★	★
Depression Screening[12]																					●	●	●	●	●	●	●	●	●	●	●
PHYSICAL EXAMINATION[13]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROCEDURES[14]																															
Newborn Blood Screening[15]		←	●	→																											
Critical Congenital Heart Defect Screening[16]		●																													
Immunization[17]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hematocrit or Hemoglobin[18]						★			●	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Lead Screening[19]							★	★	● or ★[20]		★	● or ★[20]		★	★	★	★															
Tuberculosis Testing[21]				★			★		★			★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Dyslipidemia Screening[22]												★			★		★		★	←	●	→	★	★	★	★	★	★	←	●	→
STI/HIV Screening[23]																					★	★	★	★	★	←	●	→	★	★	★
Cervical Dysplasia Screening[24]																															●
ORAL HEALTH[25]							★	★	● or ★		● or ★	● or ★	● or ★	●			●														
Fluoride Varnish[26]							←				●	→																			
ANTICIPATORY GUIDANCE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.
2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per the 2009 AAP statement "The Prenatal Visit" (http://pediatrics.aappublications.org/content/124/4/1227.full).
3. Every infant should have a newborn evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).
4. Every infant should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding infants should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in the 2012 AAP statement "Breastfeeding and the Use of Human Milk" (http://pediatrics.aappublications.org/content/129/3/e827.full). Newborn infants discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per the 2010 AAP statement "Hospital Stay for Healthy Term Newborns" (http://pediatrics.aappublications.org/content/125/2/405.full).
5. Screen, per the 2007 AAP statement "Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report" (http://pediatrics.aappublications.org/content/120/Supplement_4/S164.full).
6. Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.
7. A visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3 year olds. Instrument based screening may be used to assess risk at ages 12 and 24 months, in addition to the well visits at 3 through 5 years of age. See 2016 AAP statement, "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/1.51) and "Procedures for Evaluation of the Visual System by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/1.52).
8. All newborns should be screened, per the AAP statement "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" (http://pediatrics.aappublications.org/content/120/4/898.full).
9. See 2006 AAP statement "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (http://pediatrics.aappublications.org/content/118/1/405.full).
10. Screening should occur per the 2007 AAP statement "Identification and Evaluation of Children with Autism Spectrum Disorders" (http://pediatrics.aappublications.org/content/120/5/1183.full).
11. A recommended screening tool is available at http://www.ceasar-boston.org/CRAFFT/index.php.
12. Recommended screening using the Patient Health Questionnaire (PHQ)-2 or other tools available in the GLAD-PC toolkit and at http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf.
13. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See 2011 AAP statement "Use of Chaperones During the Physical Examination of the Pediatric Patient" (http://pediatrics.aappublications.org/content/127/5/991.full).
14. These may be modified, depending on entry point into schedule and individual need.
15. The Recommended Uniform Newborn Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/uniformscreeningpanel.pdf), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf), establish the criteria for and coverage of newborn screening procedures and programs. Follow-up must be provided, as appropriate, by the pediatrician.
16. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per the 2011 AAP statement "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease" (http://pediatrics.aappublications.org/content/129/1/190.full).
17. Schedules, per the AAP Committee on Infectious Diseases, are available at: http://aapredbook.aappublications.org/site/resources/izschedules.xhtml. Every visit should be an opportunity to update and complete a child's immunizations.
18. See 2010 AAP statement "Diagnosis and Prevention of Iron Deficiency and Iron Deficiency Anemia in Infants and Young Children (0-3 Years of Age)" (http://pediatrics.aappublications.org/content/126/5/1040.full).
19. For children at risk of lead exposure, see the 2012 CDC Advisory Committee on Childhood Lead Poisoning Prevention statement "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention" (http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf).
20. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.
21. Tuberculosis testing per recommendations of the Committee on Infectious Diseases, published in the current edition of *AAP Red Book: Report of the Committee on Infectious Diseases*. Testing should be performed on recognition of high-risk factors.
22. See AAP-endorsed 2011 guidelines from the National Heart Blood and Lung Institute, "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm).
23. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the *AAP Red Book: Report of the Committee on Infectious Diseases*. Additionally, all adolescents should be screened for HIV according to the AAP statement (http://pediatrics.aappublications.org/content/128/5/1023.full) once between the ages of 16 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually.
24. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm). Indications for pelvic examinations prior to age 21 are noted in the 2010 AAP statement "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (http://pediatrics.aappublications.org/content/126/3/583.full).
25. Assess if the child has a dental home. If no dental home is identified, perform a risk assessment (http://www2.aap.org/oralhealth/docs/RiskAssessmentTool.pdf) and refer to a dental home. If primary water source is deficient in fluoride, consider oral fluoride supplementation. Recommend brushing with fluoride toothpaste in the proper dosage for age. See 2009 AAP statement "Oral Health Risk Assessment Timing and Establishment of the Dental Home" (http://pediatrics.aappublications.org/content/111/5/1113.full), 2014 clinical report "Fluoride Use in Caries Prevention in the Primary Care Setting" (http://pediatrics.aappublications.org/content/134/3/626), and 2014 AAP statement "Maintaining and Improving the Oral Health of Young Children (http://pediatrics.aappublications.org/content/134/6/1224.full)."
26. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspsdnch.htm). Once teeth are present, fluoride varnish may be applied to all children every 3-6 months in the primary care or dental office. Indications for fluoride use are noted in the 2014 AAP clinical report "Fluoride Use in Caries Prevention in the Primary Care Setting" (http://pediatrics.aappublications.org/content/134/3/626).

KEY ● = to be performed ★ = risk assessment to be performed with appropriate action to follow, if positive ← ● → = range during which a service may be provided

Summary of changes made to the
Bright Futures/AAP Recommendations for Preventive Pediatric Health Care

(Periodicity Schedule)

This Schedule reflects changes approved in October 2015 and published in January 2016. For updates, visit www.aap.org/periodicityschedule.

Changes made October 2015

- **Vision Screening**- The routine screening at age 18 has been changed to a risk assessment.
- Footnote 7 has been updated to read, "A visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3 year olds. Instrument based screening may be used to assess risk at ages 12 and 24 months, in addition to the well visits at 3 through 5 years of age. See 2016 AAP statement, "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (http://pediatrics.aappublications.org/content/137/1/1.51) and "Procedures for Evaluation of the Visual System by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/1.52).

Changes made May 2015

- **Oral Health**- A subheading has been added for fluoride varnish, with a recommendation from 6 months through 5 years.
- Footnote 25 wording has been edited and also includes reference to the 2014 clinical report, "Fluoride Use in Caries Prevention in the Primary Care Setting" (http://pediatrics.aappublications.org/content/134/3/626) and 2014 policy statement, "Maintaining and Improving the Oral Health of Young Children" (http://pediatrics.aappublications.org/content/134/6/1224.full).
- Footnote 26 has been added to the new fluoride varnish subheading: See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspsdnch.htm). Once teeth are present, fluoride varnish may be applied to all children every 3-6 months in the primary care or dental office. Indications for fluoride use are noted in the 2014 AAP clinical report "Fluoride Use in Caries Prevention in the Primary Care Setting" (http://pediatrics.aappublications.org/content/134/3/626).

Changes made March 2014

Changes to Developmental/Behavioral Assessment

- **Alcohol and Drug Use Assessment**- Information regarding a recommended screening tool (CRAFFT) was added.
- **Depression**- Screening for depression at ages 11 through 21 has been added, along with suggested screening tools.

Changes to Procedures

- **Dyslipidemia screening**- An additional screening between 9 and 11 years of age has been added. The reference has been updated to the AAP-endorsed National Heart Blood and Lung Institute policy (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm).
- **Hematocrit or hemoglobin**- A risk assessment has been added at 15 and 30 months. The reference has been updated to the current AAP policy (http://pediatrics.aappublications.org/content/126/5/1040.full).
- **STI/HIV screening**- A screen for HIV has been added between 16 and 18 years. Information on screening adolescents for HIV has been added in the footnotes. STI screening now references recommendations made in the AAP Red Book. This category was previously titled "STI Screening."
- **Cervical dysplasia**- Adolescents should no longer be routinely screened for cervical dysplasia until age 21. Indications for pelvic exams prior to age 21 are noted in the 2010 AAP statement "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (http://pediatrics.aappublications.org/content/126/3/583.full).
- **Critical Congenital Heart Disease-** Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per the 2011 AAP statement, "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease" (http://pediatrics.aappublications.org/content/129/1/190.full).

See www.aap.org/periodicityschedule for additional updates made to footnotes and references in March 2014.

Section 4.0

Biennial Review

Novel Treatments

Question: Should HERC adopt changes to the Prioritized List that addresses novel treatments with marginal clinical benefit, low cost-effectiveness, and/or very high cost?

Question source: Health Evidence Review Commission Staff, P&T

Issue: Many novel treatments emerge that may be high cost without necessarily offering much incremental benefit over existing treatments. Some novel treatments may not meet clinically important effectiveness criteria that would justify having a treatment be prioritized very high on the Prioritized List. There is precedent for the Prioritized List to have some treatments for conditions both above and below the funding line (e.g. surgical treatments and medical treatment for back pain).

Identifying novel treatments which may have marginal benefit

HERC's process for identifying novel treatments which may be candidates for evaluation as having a marginal benefit or low cost-effectiveness would be similar to any other topic; a HERC medical director may initiate such a review or a stakeholder could also submit it for consideration. The Pharmacy and Therapeutics Committee or its staff may also identify novel prescription drugs for which these guidelines may be applicable. Experimental treatments will continue to be left off of the Prioritized List as such treatments are not to be covered per Medicaid regulations.

Mechanisms for prioritizing treatments with marginal benefit on appropriate lines

Professional services of marginal benefit that can be identified by a CPT or HCPCS code (such as surgeries and physician-administered drugs) can be managed using pairings on a low prioritized line. If the diagnosis code does not already appear on an appropriately low prioritized line, both the diagnosis code and procedure code can be added to the new lines, lines for conditions with minimally effective treatments or no treatment necessary (Lines 653-665) or other lines created for such cases.

Ancillary (e.g., outpatient prescription drugs, durable medical equipment and supplies, adjunctive procedures) and diagnostic services (e.g., labs, imaging) can be addressed with ancillary and diagnostic guideline notes. In the case of outpatient prescription drugs, HERC would need to create one or more new ancillary guideline notes. As HERC is statutorily prohibited from conducting drug class evidence reviews or medical technology assessments solely of a prescription drug, the HERC would need to rely on reports developed by other groups. As many novel treatments are prescription drugs, the HERC can rely on drug class reviews conducted by Oregon's Pharmacy and Therapeutics Committee or other reputable sources. These reviews would speak to the appropriate indications for the medications and describe their effects, including the magnitude of the effect. Based on the clinical importance of the effects/cost-effectiveness of the drugs in question, the HERC could then create one or more ancillary guidelines, attaching them to specific unfunded lines, if appropriate.

Recommendations:

Create a new statement of intent as follows:

STATEMENT OF INTENT 3, THERAPIES WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

i. Marginal or clinically unimportant benefit
ii. Very high cost in which the cost does not justify the benefit
iii. Significantly greater cost compared to alternate therapies when both have similar benefit
iv. Significant budget impact that could affect the overall Prioritized List funding level

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics.

As codes for prescription drugs, durable medical equipment & supplies, certain adjunctive procedures and other ancillary services are not typically included on the Prioritized List and are not always billed in conjunction with diagnosis codes, it is more difficult to indicate the importance of these services through the prioritization process. Through evidence reviews conducted by one of its subcommittees, the Pharmacy and Therapeutics Committee, or other reputable sources and based on these reviews, HERC prioritizes such services regarded as having low importance when prescribed for certain conditions on Line XXX or Line YYY and lists the relevant condition/treatment pairings in Guideline Notes AAA or BBB.

Create two new lines as follows:

Line XXX
CONDITION: CONDITIONS FOR WHICH CERTAIN TREATMENTS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
TREATMENT: MEDICAL AND SURGICAL TREATMENT

Ranking: There are many scenarios which may place different condition/treatment pairings on this line, so this line would need to be hand-ranked as opposed to being able to come up with a composite line score. Staff suggests that this new line be ranked around Line 500.

Line YYY
CONDITION: CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
TREATMENT: MEDICAL AND SURGICAL TREATMENT

Ranking: If there is evidence indicating there is no clinical benefit to the treatment or harms outweigh benefits, staff suggests that this new line be ranked as the last line on the list.

Create two new guideline notes as follows:

GUIDELINE NOTE AAA, TREATMENTS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following treatments are prioritized on Line XXX for the conditions listed here:

CONDITION	PRESCRIPTION DRUG
e.g., Obesity	All prescription drugs
e.g., Cancer of the liver, lung or prostate; hemangiomas	Proton beam therapy
Various	e.g., Treatments previously review by HERC that were found to be no more effective that treatments prioritized higher on the list but cost significantly more

GUIDELINE NOTE BBB, TREATMENTS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following treatments are prioritized on Line YYY, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, for the conditions listed here:

CONDITION	TREATMENT
e.g., Obstructive sleep apnea	Tongue base suspension surgery (CPT 41512)
e.g., Bladder incontinence	Tibeal nerve stimulation (CPT 64566)
e.g., Glaucoma	Transluminal dilation of aqueous outflow canal (CPT 66174-66175)
e.g., All conditions except Pompeii's disease	Enzyme replacement therapy
Various	e.g., Treatments previously reviewed by HERC that were found to have insufficient evidence of effectiveness

Cost-effectiveness Issue Summary

Question**:** Should HERC deliberate on general guidelines for cost-effectiveness?

Question Source: HERC Staff

Issue: Historically the HERC has not used a pre-defined threshold for cost-effectiveness to determine placement on the Prioritized List. With the potential adoption of the new guideline on novel treatments with marginal clinical benefit or low cost-effectiveness, HERC may wish to consider having a general discussion of what may define low cost-effectiveness.

It has been years since HERC discussed cost-effectiveness thresholds. In the biennial report, HERC has previously used the following Figure 1.9. The specific thresholds of cost-effectiveness have not been revised since 2004.

HERC may also wish to update the language in Figure 1.9 around the language about weak, moderate, strong, and compelling "evidence" for adoption (or rejection).

The potential biennial list changes related to novel treatments with marginal clinical benefit or low cost-effectiveness are going to beg the questions: What is low cost-effectiveness? What is very high cost in which the cost does not justify the benefit? What is significantly greater cost compared to alternative therapies?

In the statement of intent, these exact thresholds are not spelled out. Staff would propose that spelling them out clearly would be challenging, as each topic is going to need to be highly individualized.

The question then is whether VbBS/HERC have a general shared agreement as to what these definitions may be and is it necessary, or even possible, to further define them? Or will it be best to address each of these on an individual basis?

FIGURE 1.9
PROCESS FOR INCORPORATING INFORMATION ON CLINCAL INFORMATION AND COST-EFFECTIVENESS INTO THE PRIORITIZED LIST

HERC will review evidence as outlined in Figure 1.9. Evidence regarding the effectiveness of a treatment will be used according to the following algorithm:

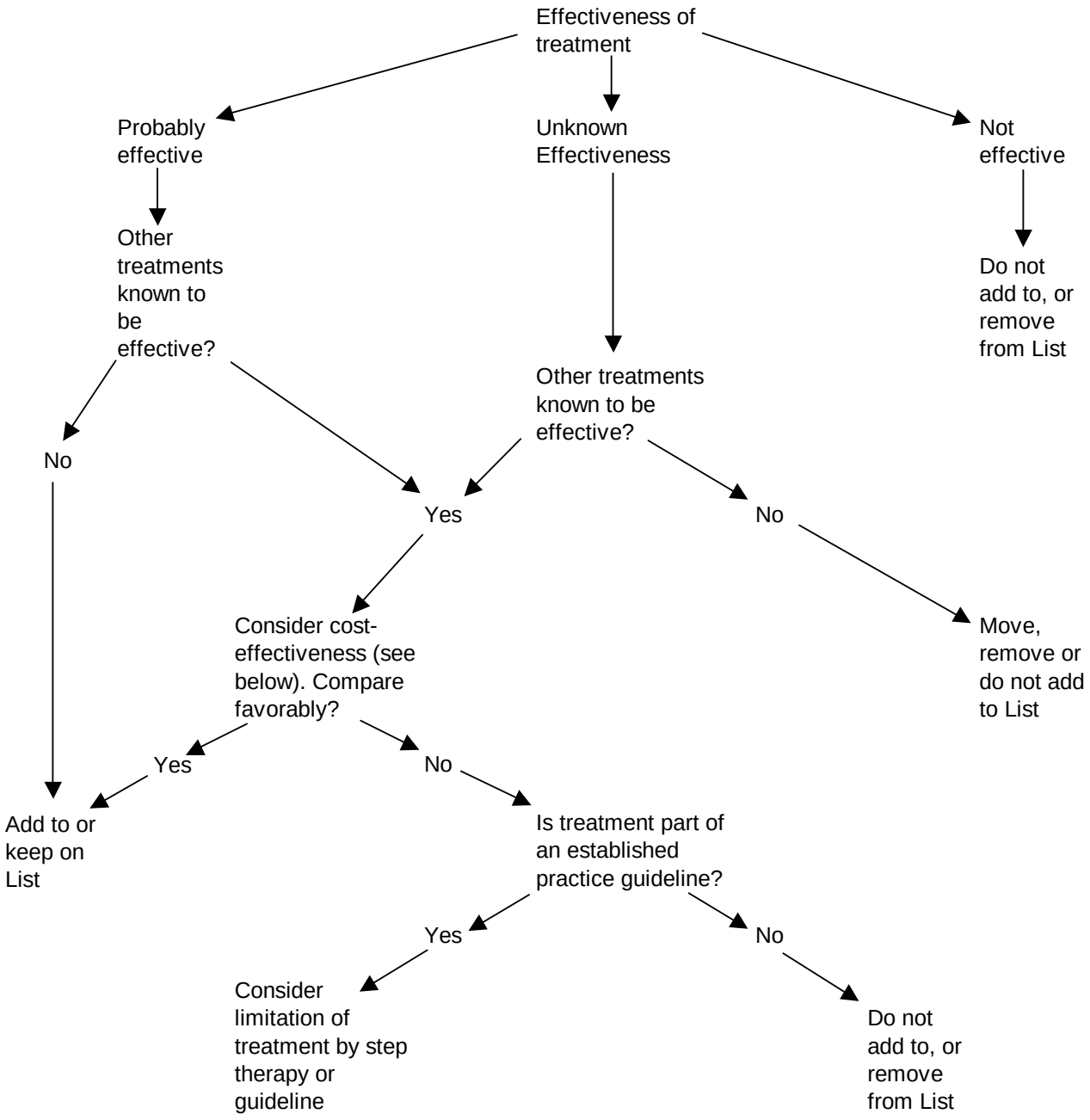

FIGURE 1.9 (CONT'D)
PROCESS FOR INCORPORATING INFORMATION ON CLINCAL INFORMATION AND COST-EFFECTIVENESS INTO THE PRIORITIZED LIST

The cost of a technology will be considered according to the grading scale below, with "A" representing compelling evidence for adoption, "B" representing strong evidence for adoption, "C" representing moderate evidence for adoption, "D" representing weak evidence for adoption and "E" being compelling evidence for rejection:

- A = more effective and cheaper than existing technology
- B = more effective and costs < $25,000/LYS or QALY > existing technology
- C = more effective and costs $25,000 to $125,000/LYS or QALY > existing technology
- D = more effective and costs > $125,000/LYS or QALY > existing technology
- E = less or equally as effective and more costly than existing technology

Background

Marseille, 2015 http://www.who.int/bulletin/volumes/93/2/14-138206/en/

- WHO Bulletin discussing issues related to approaching cost-effectiveness and willingness to pay
- Estimates of costs, health effects and ICERs provide clear guidance to policy-makers in three situations: (i) when the health-effect target is specified by policy-makers and the aim of the cost–effectiveness analysis is to minimize the expenditure needed to achieve that target; (ii) when a budget constraint is specified by policy-makers and the aim is to maximize the health benefits while keeping expenditure within budget; and (iii) when policy-makers have specified an explicit standard or threshold for what should be considered cost–effective.
- Three general approaches have been used: (i) thresholds based on per capita national incomes; (ii) benchmark interventions and (iii) league tables. In recent years, the most common approach has involved the use of thresholds based on per capita gross domestic product (GDP).
- 3 approaches and their limitations
    - Threshold approach – 2 to 3 times the per capita national income
        - Even if something is cost-effective, it may still not be the most useful priority for a country's budget. There may be other more impactful interventions.
        - It is too easy to reach the threshold
        - Social willingness to pay – an untested assumption

        - Affordability is not adequately appraised – highly prevalent conditions are a case in point
    - Benchmark interventions – $50,000/100,000/150,000 is the benchmark and so for anything below that, adoption is justified
        - Benchmarks may not represent willingness to pay (could have been based on political decisions, don't take into account opportunity costs or change in burden of disease)
        - Does not address alternatives that may be more cost-effective
            - Optimally would need to consider a range of interventions with ICERs
    - League tables – focus on largest health impact for the budget. The league-table approach is based on the principle that, for any budget, health outcomes are maximized if selection of the options for implementation begins at the top of the league table – i.e. with the option with the lowest ICER – and then moves down the list, to interventions with successively higher ratios, until the budget is exhausted.
        - ICERS may not be available for many interventions
        - The tables are also limited in the factors they include (e.g., missing the size of the affected population, whether the intervention is scalable, the health benefit per recipient and the degree of uncertainty around the ICERs)
    - Additional limitations: The comparators have to be appropriate. There is enormous between-study variability in CEA estimates.
- Authors conclusions: Need to consider both disease burden and the budget

Neumann, 2014

- NEJM perspective article about cost-effectiveness thresholds
- $50,000 per QALY has been standard although its origin is unclear (dialysis for ESRD in 1970s?) and widespread popularity started in the 1990s.
- Willingness to pay depends on a healthcare budget
- Not a hard stop. Generally <$50,000 per QALY is "favorable" v >$50,000 is "unfavorable"
- Some economists have argued for a higher thresholds

Cost-Effectiveness Thresholds Referenced by Authors of U.S.-Based Cost-Utility Analyses, 1990–2012.*			
Threshold	**1990–1999 Analyses (N=207)**	**2000–2009 Analyses (N=851)**	**2010–2012 Analyses (N=444)**
		percent	
$50,000 per QALY	19.3	36.6	36.9
$100,000 per QALY	6.3	7.8	16.9
Both $50,000 and $100,000 per QALY	3.9	19.9	23.7
Other	18.4	10.6	7.4
No threshold referenced	51.9	25.1	15.3

* Data are from the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org). QALY denotes quality-adjusted life-year.

- The opportunity costs of making health care decisions are rarely known
- Authors recommend having multiple thresholds ($50k, $100k or $150k) depending on the available resources for the relevant decision maker and possible other uses of those resources

Maciosek, 2010

- Evaluates costs of adopting a bundle of 20 evidence-based clinical preventive services (e.g. breast cancer screening, colon cancer screening, hypertension screening)
- Demonstrates that very few preventive health care services are actually cost-saving in terms of annual net medical costs per person per year:
    - Childhood immunizations (more than 3 times any of the others)
    - Pneumococcal immunization
    - Discussing daily aspirin use
    - Smoking cessation advice and assistance
    - Alcohol screening and brief counseling
    - Obesity screening
    - Vision screening (adults)

Neumann, 2010

- Cost-effectiveness analysis registry review to identify low value services
- Define “low-value” – low value goes beyond waste and inappropriate care to include interventions that deliver positive but limited benefits relative to their costs. For purposes of this study, we defined low-value services to be those that make health worse (without saving money) or those that cost at least $100,000 per QALY gained

- Methods: We searched the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org) to identify examples of low-value services. We restricted our attention to papers published since 2000. We supplemented this literature review with a list of services recently rejected by NICE for coverage by the UK's National Health Service.
- Challenges relate to the underlying evidence base, the applicability of the study to the target population, and the strength of the cost-effectiveness evidence.
- Example services with low cost-effectiveness

Table 1. Selected Services With Relatively Unfavorable Cost-Effectiveness

Service	Compared With:	Cost-Effectiveness (2007 US Dollars)
Lung volume reduction surgery	Continued medical treatment	$100,000-$300,000 per QALY[40]
Cetuximab for the treatment of metastatic colorectal cancer after failure of chemotherapy	Active/best supportive care	$110,000-$410,000 per QALY[41,42]
Anastrozole in women with estrogen-receptor positive breast cancer	Tamoxifen	$270,000 per QALY[43]
Transmyocardial revascularization for patients with severe angina refractory to standard medical therapy	Continued medical therapy	$440,000 per QALY[44]
Left ventricular assist devices	Optimal medical care	$500,000-$1.4 million per QALY[45]
Pemetrexed to treat non–small-cell lung cancer	Docetaxel Erlotinib and docetaxel	$870,000 per QALY[46] Increases cost and results in worse health outcomes[47]
Positron emission tomography in Alzheimer's disease	Standard examination	Increases cost and results in worse health outcomes[48]

QALY indicates quality-adjusted life-year.

Chambers, 2010

- Evaluation of the use of cost-effectiveness in Medicare National Coverage Determinations (NCDs)
- 1999-2007, N= 103
- Reviewed the cost-effectiveness of the interventions included in NCD
- Results: Of the 64 coverage decisions determined to have a corresponding cost-effectiveness estimate, 49 were associated with a positive coverage decision and 15 with a noncoverage decision. Of the positive decisions, 20 were associated with an economic evaluation that estimated the intervention to be dominant (costs less and was more effective than the alternative), 12 with an incremental cost-effectiveness ratio (ICER) of less than $50,000, 8 with an ICER greater than $50,000 but less than $100,000, and 9 with an ICER greater than $100,000. Fourteen of the sample of 64 decision memos cited or discussed cost-effectiveness information.
- Author conclusions: CMS is covering a number of interventions that do not appear to be cost-effective, suggesting that resources could be allocated more efficiently. Although

the authors identified several instances where cost-effectiveness evidence was cited in NCDs, they found no clear evidence of an implicit threshold.

National Institute for Clinical Excellence (NICE) (from https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 and NICE blog https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold)

- Our independent committees use a threshold for recommending treatments of between £20,000 and £30,000 per quality adjusted life year. We think it represents a reasonable compromise between ensuring everyone has fair and equitable access to the NHS and enabling access to new and innovative treatments.
- At this threshold, NICE currently recommends 8 out of 10 drugs or other technologies that it appraises, including 6 out of 10 cancer drugs. So we are careful about protecting, as much as we can, the interests of those who don't benefit from the newest treatments.
- The focus on cost-effectiveness analysis is justified by the Institute's focus on maximising health gains from a fixed NHS and personal social services budget and the more extensive use and publication of these methods compared with cost–benefit analysis. Currently, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects.

HERC Staff Summary

There are multiple ways to address cost-effectiveness. The "benchmark approach" of $50,000 per QALY still appears to be the most common in the US, although there is a trend towards higher amounts per QALY in US cost-effectiveness literature. Medicare does not appear to abide by a strict cutoff. NICE in the UK still uses 20,000-30,000 pounds as their cutoff (roughly USD $25,000-37,000).

The current Figure 1.9 includes an algorithm, when previously HERC decided to no longer use an algorithm for decision-making because of an inability to capture the necessary nuance. It also includes specific cost-effectiveness thresholds that no longer seem to relate to the current literature.

HERC Staff Recommendations

1) Delete Figure 1.9 from the upcoming biennial report

2) Discuss if there will be a generally accepted definition of low cost-effectiveness, or very high cost, or significantly higher cost compared to other alternative treatments.

Section 5.0

New Discussion Items

Question: Should pharmacogenetics testing be covered to help guide medication decisions for patients with depression or similar mood disorders; if so, for which patient groups and with what restrictions?

Question source: EbGS

Issue: Pharmacogenetics testing for depression was raised as a topic for EbGS to examine through the coverage guidance process. However, it was determined that Washington HTA was undergoing a major review of this topic and therefore a coverage guidance review would be redundant. EbGS referred this topic to VBBS to consider, with review of the WaHTA report.

Pharmacogenetics testing is the process of testing selected genes believed to be associated with drug response or potential adverse reactions. Available panels have some overlap in the genes included in each panel, but not all panels test the same genes. Potential uses for the information gleaned from both types of tests include drug and dose selection for initiating or changing medications with the intent to improve patient outcomes and experiences with treatment.

The Genetics Advisory Panel discussed this topic at their September 2016 meeting. The advisory panel felt that it was probably premature to cover such testing, and it was unclear how the information obtained from such testing was best utilized.

Current Prioritized List status
CPT 81479 (Unlisted molecular pathology procedure) is on the Suspend for Review File
81225-81227 (CYP2C19 (cytochrome P450…) (eg, drug metabolism), gene analysis) are all on the Services Recommended for Non-Coverage Table

Evidence

1) **WaHTA 2016**, Pharmacogenomic testing (PGx) for selected conditions **(Report here: http://www.hca.wa.gov/assets/program/pharmacogenomics-final-rpt-20161209.pdf)**
    a. N=14 studies
        i. Examined use in major depression, schizophrenia, anxiety, ADHD, bipolar disorder and substance use disorder
        ii. Included studies of patients being prescribed medications for psychiatric disorders; no differentiation made based on treatment naïve patients vs single medication failure vs multiple medication failure
        iii. Studies examined gene panels and single gene testing
    b. Impact of PGx on clinical decision making
        i. N=4 studies (2 fair quality RCTs [N=74, 51], 1 fair quality controlled trial [N=51], 1 poor quality comparative study [N=58])
            1. all examining decision making in patients with depression
        i. Overall quality of evidence rated low due to small patient populations, patient population limited in terms of race
        ii. Limited results suggest that PGx test results, whether single-gene or interpretive panels, may change prescribing patterns in favor of PGx recommendations compared with treatment as usual.

iii. While management change is a necessary step toward improving patient outcomes, it is not sufficient to support a conclusion of clinical benefit.

c. Impact on clinical outcomes
    i. Remission
        1. N=4 studies (2 fair quality RCTs [N=51, 148], 1 fair non-randomized prospected controlled trial [N=227], 1 poor quality retrospective comparative trial [N=116])
            a. All examined patients with depression
        2. In all studies, the direction of results suggests that genotyped patients are more likely to obtain remission. But results are not consistently statistically significant and in 1 study may not be clinically relevant. In summary, despite consistency of results favoring improved remission rates as a result of genotyping, the quality of the evidence is low and our confidence that the results represent a true effect is therefore also low.
    ii. Response to treatment
        1. Depression: N=4 studies (1 fair quality RCT [N=51], 2 fair non-randomized prospected controlled trials [N=227, 51], 1 poor quality comparative trial [N=46])
        2. Any psychotic disorder: N=1 study (poor quality comparative study [N=182])
        3. Alcohol use: N=1 study (fair quality observational study [N=221])
        4. Results are in the direction of improved response for genotyped patients. Only 1 study used defined measures of response and obtained statistically significant results. In the naltrexone trial for alcohol use, results were opposite those of prior studies, although not statistically significant
        1. Overall, the results for response to treatment, comparing pharmacogenomic testing–informed prescribing with treatment as usual, lack consistency, are limited in some cases by lack of acceptable measures of response, or were underpowered. The overall quality of the evidence is low.
        2. Best results are reported by a fair-quality prospective controlled trial that used 3 such measures of response and showed that patients whose prescribing physicians had access to results from a U.S.-based pharmacogenomic genotyping panel were statistically significantly more likely to respond than control patients who were prescribed treatment as usual for 8 weeks.
    iii. Adherence, Tolerance, Adverse Events
        1. Depression: 1 fair quality RCT (N=148)
            a. non-genotyped control patients were less tolerant of medications, statistically significantly more often requiring dose reduction or cessation. In addition, genotyped patients took sick leave less often, and took leave times of shorter duration when needed, compared with non-genotyped patients.
        2. Any psychotic disorder: 3 poor quality comparative studies (N=182, 333, 12,542)

a. In 2 of 3 studies, results indicate increased tolerance of medications when prescribed with knowledge of PGx results.

3. Alcohol use: 1 fair quality observational study (N=221)
    a. In the naltrexone trial for alcohol use, adherence was lower for carriers of the asp40 allele, reported to moderate the response in prior studies.

iv. Hospital stay/healthcare utilization
1. 1 poor quality retrospective comparative study (N=116)
    a. indicate PGx for *ABCB1* variants may result in better anti-depressant dosing and shorter hospital stays; not generalizable

d. Cost effectiveness
i. Cost modeling: N=4 studies (quality not given): 1 depression, 2 mixed psychiatric disorders, 1 schizophrenia. Total patients: 1921 (experimental group) vs 11,253 (control group)
1. Results are not comparable across studies. Each used different types of sources, enrolled pts with different indications, and used different measures for cost comparison.
2. Results of 3 of 4 cost-comparison studies suggest that employment of PGx testing is associated with reduced total costs for healthcare; however, results in 1 study suggested that significant cost benefits of PGx testing may be limited to extreme metabolizers (poor or ultrarapid).

ii. Cost-effectiveness: 2 modeling studies
1. One study found PGx testing not to be cost-effective; 1 modeling study of a hypothetical patient cohort estimated an increased overall cost of healthcare with PGx vs Ctl for an incremental benefit in QALW.

iii. Cost-utility: 1 study (N=323), types of diagnoses not given
1. Utility increases with decreases in the number of changes in meds or ↓ times for dosage adjustments.

e. Overall summary of evidence:
i. Pharmacogenomic test results consistently led medication treatment prescribers to change their treatment decisions compared with treatment as usual but the overall quality of evidence was low. While management change is a necessary step toward improving patient outcomes, it is not sufficient to support a conclusion of clinical benefit.

ii. The evidence supporting the use pharmacogenomic test results for patient management and their impact on patient outcomes is extremely limited and compromised and is considered to be of low to very low quality, depending on the outcome measured. As such, the evidence is insufficient for conclusions regarding clinical use.
1. Studies are underpowered, had differing or inappropriate definitions of clinical remission or response, used differing genetic panels (some not available in the US), had populations that were not generalizable, had high loss to follow up, or were otherwise poorly designed

iii. Economic study results in some cases suggested cost-effectiveness but lacked consistency overall. Furthermore, economic analyses are limited by the low quality of the available evidence base and the applicability of the evidence selected to create the various models employed.

iv. Of the practice guidelines that mention pharmacogenomic testing at all, most make no formal recommendations for use, but rather indicate a need for future research. Some guidelines suggest that pharmacogenomic testing in combination with therapeutic drug monitoring may be beneficial in certain circumstances.

Submitted evidence disposition

1) Herbild 2013: included in WaHTA report
2) Liu 2011: studies a single gene variant
3) Ramsey 2011: studies a single gene variant

Other policies

1) Aetna and most BCBS plans consider pharmacogenetics testing for antidepressant management to be experimental
2) Cigna has limited coverage of single gene tests when the outcome is expected to affect clinical management

HERC staff summary:

The major evidence based review of pharmacogenetic testing for psychiatric medication management did not find sufficient evidence of clinical benefit to support its use for panel testing or single gene testing.

HERC staff recommendations:

1) Do not add coverage for pharmacogenetics testing for management of any psychiatric condition (e.g. depression, schizophrenia, alcohol abuse, etc.)
2) Adopt the following diagnostic guideline

DIAGNOSTIC GUIDELINE DXX, PHARMACOGENETICS TESTING FOR PSYCHIATRIC MEDICATION MANAGEMENT

Pharmacogenetics testing for management of psychiatric medications is not a covered service.

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We respectfully submit the following comments for review by the Genetics Advisory Panel on October 5th, 2016 based on the agenda item: "**Discussion regarding pharmacogenetic testing"**

The **GeneSight® Psychotropic** test helps healthcare providers determine the right medication for individuals suffering from mental illness based on their unique genetic information. GeneSight Psychotropic is a unique "combinatorial" pharmacogenomic test utilizing patented and proprietary technology. The test collectively integrates and weights the importance of multiple genes affecting an individual's ability to tolerate and respond to neuropsychiatric medications and conveys to healthcare providers a clear picture of genetically optimal medications for their patients with mental illness. The user-friendly GeneSight report helps guide healthcare providers' medication decisions so their patients may start taking the right medication sooner, thereby improving clinical and economic outcomes.

- Of the patients diagnosed with a mental illness who seek treatment and are prescribed a neuropsychiatric medication, about half will fail the first one and subsequently begin an often lengthy odyssey of medication trial-and-error.[1]
- Use of the GeneSight test to guide patient neuropsychiatric medication selection has been proven in clinical studies to improve patient symptoms by greater than 70%.[2]
- Treatment guided by GeneSight results in an average $2,500 annual healthcare savings per patient (drug and medical spend).[3,4]
- GeneSight is the only combinatorial pharmacogenomic test for antidepressant medication guidance approved for coverage by Medicare.[5]
- A one in four lifetime prevalence of mental illness exists in the U.S. with related medication misuse and non-adherence costs topping $140 billion annually.[6]
- Significant additional healthcare costs are incurred along the way for drugs and other medical expenses related to the mental illness and common comorbidities.[6]
- GeneSight Psychotropic has been ordered by over 12,000 clinicians, and actionable results have been delivered for over 350,000 patients throughout the U.S.
- As a genetic test, GeneSight Psychotropic is performed once per lifetime per member.
- The clinical validity, utility and cost-effectiveness of GeneSight Psychotropic have been clearly demonstrated in multiple peer-reviewed and published studies.[2,3,4,7,8,9]

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Pharmacist Medication Management

Question: Should the guideline for pharmacist medication management be modified to remove the requirement that services require the referral from a licensed provider?

Question source: OHA, Oregon Pharmacy Association

Issue: Guideline Note 64 current requires referral from a licensed provider or health plan for payment of pharmacist medication management. OHA received a request from the Oregon Pharmacy Association to remove this clause from the guideline.

From OPA:

> This is now outdated language as pharmacists have provider status in Oregon and may initiate therapy and patient assessment on their own. CCOs may choose to require referral for inclusion or payment, but we don't want to mandate this by rule. I can see a scenario (like in my organization), where pharmacists are identifying qualifying patients and initiating medication therapy management on their own. We want to make sure we do not present extra administrative burdens or decrease access to these services due to delay.

Currently, pharmacists in Oregon can independently prescribe birth control, immunizations, and limited other medications such as naloxone and epinephrine. Pharmacists can also provide medication reviews and recommendations. These changes in practice have occurred through legislative action in the last few years.

HERC/HSC history:
99605-99607 (pharmacist medication management codes) were added to the list in 2007 as new 2008 CPT codes. At that time, there was discussion that pharmacists might need to be credentialed if these codes were added, and therefore the clause requiring a referral was added. There was debate about who qualifies as a pharmacist (clinical, PharmD, etc.) at the 2007 meeting. Initially, the guideline had a clause specifying the training required to be considered a pharmacist, but this was later struck out.

From Caryn Mickelson, PharmD, Director of Pharmacy Services for Western Oregon Advanced Health and Southern Region Delegate on the Board of Directors for the Oregon State Pharmacy Association:

> Thank you for reaching out regarding pharmacist provider status and guideline note 64. I am supportive of removing the referral language in Guideline Note 64. House Bill 2028 established provider status for Oregon pharmacists, so I am happy to see we are moving forward with making clinical pharmacy services readily available for our OHP population! It's my understanding that if a pharmacist has a DMAP provider ID number the CCO is able to reimburse for provided services and that no additional credentialing is required. Last I heard, OHA has clarified the process for corporate pharmacy chains to submit applications for DMAP provider ID numbers for their employed pharmacists, and therefore billings for oral contraceptive prescribing should be received soon.
>
> I am also supportive of removing the clause about collaboration with the physician or licensed provider. I don't think we should make the guideline note more restrictive than the Oregon law, and the law does not require collaboration or referral. I am supportive of including language *encouraging* collaboration with the PCP, but I don't think it should be a requirement.

CCO Pharmacy Directors' meeting 1/26/17

The CCO Pharmacy Directors' were in favor of the HERC staff suggested guideline edits. The group discussed deletion of the guideline, but the group felt that the guideline should be kept with the suggested edits. The group felt that the guideline was useful as it clearly states that pharmacist medication management is a covered service. Smits noted that the CPT codes for pharmacist medication management are included on the Prioritized List and therefore are clearly covered services. Pharmacists use E&M codes for services such as prescribing birth control. There is nothing in the current guideline that would prohibit the use of E&M codes when used appropriately. There were no other suggested edits or additions.

HERC staff recommendation:

1) Modify GN64 as shown below

GUIDELINE NOTE 64, PHARMACIST MEDICATION MANAGEMENT

Included on all lines with evaluation & management (E&M) codes

Pharmacy medication management services must be provided by a pharmacist who has:

1) A current and unrestricted license to practice as a pharmacist in Oregon
2) ~~Services must be provided based on referral from a physician or licensed provider or health plan.~~
3) Documentation must be provided for each consultation and must reflect ~~collaboration~~ communication with the patient's primary care ~~physician or licensed~~ provider. Documentation should model SOAP charting; must include patient history, provider assessment and treatment plan; follow up instructions; be adequate so that the information provided supports the assessment and plan; and must be retained in the patient's medical record and be retrievable

Breast Reduction for Macromastia
Impact on Neck and Back Pain

Question: Is breast reduction mammoplasty for macromastia an effective treatment for neck and/or back pain?

Question source: OHP Medical Directors

Issue: Currently, macromastia is on an uncovered line on the Prioritized List, Line 653 MACROMASTIA/BREAST REDUCTION. Breast reduction is covered on the breast cancer line for symmetry of the reconstructed breast and natural breast; this coverage is mandated by federal rule. It is also covered as treatment for gender dysphoria. Back pain moved to a covered line on July 1, 2016. Since that time, the CCOs have received requests for breast reduction for macromastia as treatment for the covered comorbid condition of neck or back pain. The OHP Medical Directors requested a review of the effectiveness of breast reduction for macromastia on neck and/or back pain and guidance on whether neck or back pain should be considered a qualifying co-morbidity for macromastia treatment.

Macromastia is defined as large breasts, generally considered larger than a D cup although various other definitions may be used. Macromastia can cause various physical symptoms, including headache, neck pain, back pain, and shoulder pain. Breast reduction is used to reduce the size of the breasts, and is one of the most commonly performed cosmetic surgeries in the US.

Current Prioritized List status
CPT 19318 (Reduction mammoplasty) is on lines 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER, 317 GENDER DYSPHORIA/TRANSEXUALISM, and 563 MACROMASTIA.

ICD-10 N62 (Hypertrophy of breast) is on lines 563 MACROMASTIA and 646 GYNECOMASTIA

Evidence
Effectiveness

1) **CADTH 2014**, rapid review of clinical effectiveness of breast reduction surgery for macromastia https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RB0720%20Breast%20Reduction%20for%20Back%20Pain%20final.pdf
    a. One systematic review (**Singh 2012**, see below), three non-randomized studies (Foreman 2009—in Singh 2012; **Valtonen 2014**; **Strong 2015**), and three evidence-based guidelines
    b. Included outcomes: Clinical effectiveness (i.e., reduction in neck, shoulder, and upper back pain)
    c. Overall summary: The identified systematic review found that women who underwent breast reduction surgery had improved outcomes regarding musculoskeletal pain, breathing, sleep, and headaches. One non-randomized study found that women who had larger breast tissue resection volumes had more often experienced pre-operative back pain, breast pain, shoulder grooves, rashes under the breasts, poor posture, and exercise intolerance than those who went on to have smaller resections; however, symptoms improved in both groups postoperatively. The authors concluded that breast reduction surgery improved a variety of symptoms, regardless of body surface-area calculated adjustments and breast tissue resection volume. The remaining two non-

randomized studies also found a postoperative improvement in breast-related symptoms, including quality of life, frequency of pain, and low-back compressive forces.

d. One guideline suggests that breast reduction should be considered when resection weight is 500 grams or more, and that surgery is not to be considered in patients with a body mass index greater than 27.5. Two guidelines from the American Society of Plastic Surgeons state that resection volume is unrelated to symptom relief, and there is inconclusive evidence regarding the risk of complication associated with body mass index; ability to undergo surgery, and resection volume, should be at the discretion of the surgeon.

a. The guidelines suggest breast reduction surgery be considered for patients experiencing the following symptoms:
    a. back pain (upper or unspecified), neck pain, and shoulder pain
    b. intertrigo, especially if unresponsive to medical intervention
    c. shoulder grooving from bra straps
    d. socially or emotionally bothered by large breasts
    e. physical activity limited by breast size
    f. breasts are low hanging, with stretched skin and enlarged areolas
    g. when breasts are unsupported, nipples hang below the breast crease
    h. acquired thoracic kyphosis
    i. chronic breast pain
    j. headache
    k. paresthesia of the upper extremities
    l. and congenital breast deformity

2) **Singh 2012**, systematic review of benefits of reduction mammoplasty
    a. Included in CADTH report above
    b. N=7 studies (331 patients total)
        i. N=2 studies (103 patients) with neck or back pain as symptom leading to breast reduction
            1. Foreman et al 2009
                a. N=11 patients
                b. Found 35% reduction postoperative low compressive back force; postoperative decrease in disability; 76% improvement in postoperative Functional Rating Index. Level IIB evidence
            2. Friere et al 2007
                a. N=92 patients
                b. Per Singh, had a surgical group and a control group
                c. Unable to obtain actual citation/article for evaluation
                d. “Patients undergoing breast reduction had decreased back, shoulder, and neck pain frequency”

3) **Perez-Panzano 2016**, prospective cohort study of outcomes of breast reduction
    a. N=121 patients, no controls
    b. The most common symptom was pain
    c. A total of 27.3% of the patients suffered complications and 30.60% suffered sequelae
    d. Our results show an improvement in symptoms ($p < 0.001$) and quality of life ($p < 0.001$ to $p = 0.002$) 1 month after and 1 year after breast reduction compared with the preoperative situation.
    e. One year after surgery, the majority of patients were satisfied with the outcome (96.6%)

   f. Conclusions: Breast reduction is highly efficient in resolving symptoms and in improving quality of life. It leads to a high level of short- and long-term satisfaction irrespective of each patient's individual characteristics.

4) **Strong 2015**; cohort study of impact of breast reduction for macromastia on various symptoms depending on volume of breast reduced
   a. N=410 patients, cohort study with no controls
   b. For back pain, analysis showed that preoperative back pain was a significantly more frequent finding in patients who had between ''476-550 g'' and ''More than 550 g'' tissue removed per breast when compared with those who had ''Less than 251 g'' removed (P = 0.004 and 0.000, respectively). Back pain was also significantly more frequent in patients who had more than 550 g tissue removed when compared with those who had 251 to 325 g removed (P = 0.034).
   c. Back and neck pain significantly improved in all breast volume reduction groups postoperatively (P<0.05)
5) **Valtonen 2014** (unable to obtain sharable copy of study); validation study of breast symptom questionnaire
   a. N=59 patients undergoing reduction mammoplasty for macromastia
   b. Cohort study with no controls
   c. "Most patients (55 of 59) experienced a remarkable reduction of breast-related symptoms postoperatively"
   d. "Discomfort/symptoms" decreased significantly (P<0.001)
   e. Most symptoms evaluated were quality of life related, not pain related (mobility, sexual function, depression, speech, sleep, breathing, elimination, mental function, etc.)
   f. Changes in responses to questions about neck or back pain specifically were not reported
6) **Collins 2002**, prospective cohort study of effectiveness of breast reduction for macromastia
   a. N=179 operative patients, 88 controls with macromastia (cup size >D), and 96 normal controls
      i. Operative patients were recruited from patients presenting to plastic surgery offices, controls were recruited via newspaper ads offering an honorarium
   b. 50% of operative subjects reported back, shoulder or neck pain prior to surgery compared to 10% after surgery
      i. Pain Rating Index preop 26.6, post op 11.7 (similar to normal controls 11.2)
      ii. No information was given on the pain scores of the macromastia controls

Complications

1) **Fischer 2014**, evaluation of complications from NSQIP data set
   a. N=3538 patients
   b. The incidence of overall surgical complications was 5.1%.
   c. The following factors were independently associated with any surgical complications: morbid obesity (odds ratio [OR], 2.1; P < .001), active smoking (OR, 1.7; P < .001), history of dyspnea (OR, 2.0; P < .001), and resident participation (OR, 1.8; P = .01). The incidence of major surgical complications was 2.1%.
   d. Conclusions: This study demonstrates overall incidence of complications in 1 in 20 patients and a 1 in 50 incidence of a major surgical complication.

2) **Hanwright 2010**, evaluation of complications of breast reduction from NSQIP data set
    a. N=2507 patients undergoing reduction mammoplasty
    b. Overall complication rate 4.47%, no life threatening complications
    c. Patients undergoing reduction mammaplasty had a modestly elevated incidence of overall morbidity, superficial surgical site infections, and wound disruptions ($P < .05$) compared to other cosmetic breast procedures

Specialty society guidelines

1) **Kalliainen 2012**, American Society of Plastic Surgery guidelines for breast reduction
    a. Evidence indicates that resection volume is not correlated to the degree of postoperative symptom relief; thus, the criterion for reduction mammaplasty is more accurately defined by individual symptoms rather than by breast volume alone (Level II Evidence: Grade B).
    b. Evidence indicates that reduction mammaplasty is effective in reducing breast-related symptoms and improving quality of life; therefore, reduction mammaplasty should be considered for patients with symptomatic breast hypertrophy (Level I Evidence: Grade A).

Major insurance coverage:

1) All major insurers cover breast reduction for macromastia that is causing back, neck or shoulder pain that does not respond to conservative therapy and has been present for some defined length of time

Expert input:

Dr. Laurel Soot, breast surgeon

> I'm not sure what literature was reviewed but I found these two documents that have a nice reference section [Singh 2012 and Kalliainen 2012, both above]. I agree that each reference independently is not ideal but when combined it does seem that there is a real benefit in reduction of pain and improvement in QOL. The plastic surgery guidelines attached have ICD9 codes as well for reference. For what it is worth, Hayes gave it a B rating for symptom improvement and archived their report in 2014. From a cost perspective if you knew that the patient would improve physically and mentally then I think you could recoup the cost of the procedure – this is a tough group of patients and even if they have the procedure there are a lot of other issues that play a role in their overall health and mental well-being.

HERC staff summary:

There is a general lack of good quality studies on the effectiveness of breast reduction on treatment of neck and/or back pain related to macromastia. No RCTs were identified; only one study (Collins 2012) appeared to have a comparison group of any kind (Friere 2007 reportedly also had a comparison group). Most studies are cohort studies or case series. The existing literature in this area does appear to indicate that patients have significant pain relief following surgery; however, the poor quality of the literature makes it difficult to make a definitive conclusion. Additionally, the literature shows that the size of the breast and/or amount of breast tissue removed is not related to the amount of pain or pain relief. This surgery appears to have a low complication rate based on large registry studies.

HERC staff recommendation:

1) Adopt the following guideline note for line 563
   a. Reduction mammoplasty will still be covered for post-mastectomy patients and for gender dysphoria; it would be paired with macromastia but on a line below the coverage line but would no longer be allowed for treatment of the co-morbid conditions of neck and/or back pain due to lack of evidence of effectiveness

GUIDELINE NOTE XXX, BREAST REDUCTION SURGERY FOR MACROMASTIA

Line 563

Breast reduction surgery for macromastia is not covered as a treatment for neck or back pain resulting from the macromastia due to lack of evidence of effectiveness.

Additional Benefits of Reduction Mammaplasty: A Systematic Review of the Literature

Kimberly A. Singh, M.D.
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Background: Reduction mammaplasty is commonly described with regard to its qualitative benefits. The authors sought to perform a systematic review of the literature focusing on functional outcomes after reduction mammaplasty with regard to physical and psychological symptom improvement, including weight-related effects, exercise, and eating behaviors, in addition to aesthetic outcomes.
Methods: A systematic review of the English literature was performed using the PubMed database to evaluate outcomes following reduction mammaplasty from 1977 to 2010. Studies were chosen that addressed the physical and psychological benefits of reduction mammaplasty using a validated questionnaire.
Results: Women who undergo reduction mammaplasty have a functional improvement in musculoskeletal pain, headaches, sleep, and breathing. Psychological benefits are vast and include improved self-esteem, sexual function, and quality of life, in addition to less anxiety and depression. After reduction mammaplasty, women appear to exercise more and have a reduction in eating disorders.
Conclusion: The authors present a comprehensive review of the literature with regard to the physical and emotional concerns women with macromastia experience and the broad benefits reduction mammaplasty could have for their daily functions and quality of life postoperatively. (*Plast. Reconstr. Surg.* 129: 562, 2012.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

According to the American Society of Plastic Surgeons, nearly 80,000 breast reductions were performed in 2009.[1] Women typically present complaining of the physical symptoms of macromastia. Numerous studies have qualitatively described an improvement in these physical symptoms following breast reduction.[2–4] However, there is a paucity of systematic reviews of the literature addressing objective functional improvement of physical symptoms after reduction mammaplasty.

Even less common are investigations on the effect of reduction mammaplasty on weight loss, exercise, and eating behavior. Women with large breasts often find exercising difficult because of public scrutiny and physical constraints. They may even develop eating disorders in an attempt to match their breast size to the rest of their body. Although there are no formal reviews to date addressing weight loss, exercise, and eating behaviors, these issues are often central to women who present for reduction mammaplasty. Improvement of physical symptoms of reduction mammaplasty surgery can be effectively measured, but psychological improvement is harder to quantify. Women with macromastia often have diminished self-esteem, poor psychosexual function, depression, and anxiety. When these factors are coupled with the physical pain associated with macromastia and weight-related issues, the negative impact on quality of life can be substantial. By uniquely combining a literature review of the psychological benefits of reduction mammaplasty with the aforementioned functional improvement of physical symptoms, weight, and eating behavior, we are able to distinctly present a comprehensive assessment of the positive impact that reduction mammaplasty has on women's lives. The aim of this systematic review is to improve the global under-

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standing of the physical and emotional concerns women with macromastia experience, and the broad benefits that reduction mammaplasty could have on their quality of life postoperatively.

PATIENTS AND METHODS

A systematic review of the English literature was performed by means of the PubMed database using the Medical Subject Headings "breast reduction"; "reduction mammaplasty"; and "quality of life, pain, aesthetic, and outcomes" for the period between 1977 and 2010. Studies performed to evaluate outcomes after reduction mammaplasty with regard to physical symptoms, weight loss, exercise, eating behaviors, psychological symptoms, and aesthetic results were chosen. Boolean operations were then applied to the chosen terms and studies were chosen based on human studies and reported in the English language. Several references were cited after evaluation of these investigations. A single surgeon reviewed all of the references. Studies were chosen that addressed three criteria regarding reduction mammaplasty: (1) physical and psychological symptom improvement (including weight, exercise, and eating behaviors); (2) global quality-of-life improvement as reported by one or more outcomes assessments; and (3) use of a validated questionnaire. All studies chosen for review had outcomes measures that were evaluated prospectively before and after surgery and were compared with a control group. For inclusion in the section of physical symptom improvement, detailed scientific analysis was required. Level of evidence was cited for each article chosen. Because of reporting construct inconsistencies, meta-analysis could not be performed.

RESULTS

Physical Improvement

Table 1 summarizes the literature review results regarding the effect of reduction mammaplasty on physical symptom improvement.[5–11]

Physical Symptom Improvement

Improvement in Back and Neck Pain

Collins et al. suggested that the physical symptoms of macromastia should be the criteria for insurance coverage of reduction mammaplasty.[4] As such, one study evaluated the biomechanical effect of reduction mammaplasty on the lumbar spine and found a 35 percent reduction in lower back compressive force and a 76 percent decrease in self-reported disability as measured by the Functional Rating Index.[7] Another study similarly found that reduction mammaplasty improved functional capacity and relieved pain in the lower back, neck, and shoulders.[8] They looked at 100 patients seeking breast reduction, 50 of whom underwent surgery; the other 50 women served as a control group as they awaited surgery. Functional capacity was represented by activities of daily living using the Stanford Health Assessment Questionnaire, whereas a visual analogue scale was used to measure neck, shoulder, and lower back pain. Another study found a significant improvement in upper body strength and posture after reduction mammaplasty and improved pain and disability regardless of body mass index.[10] It is known that mammary hyperplasia alters a women's center of gravity, increasing cervical muscle tone and spine curvature.[12] These forces can lead to degenerative changes in the spine.[5]

Improvement in Chronic Headaches

Reduction mammaplasty may reduce chronic headaches and migraine symptoms.[6] Ducic and colleagues noted that nearly 90 percent of women presenting with macromastia complained of occipital neuralgia and chronic headaches/migraines. These women had a 50 percent reduction in headache symptoms after surgery and improved quality of life as a result of pain reduction.

Improvement in Lung Function

Starley and colleagues reported improved peak inspiratory and expiratory flow rates following reduction mammaplasty.[9] A reduction in breast mass may therefore improve chest wall compliance, which could improve exercise tolerance and should be considered in the treatment protocol for women suffering from both macromastia and respiratory conditions. This study also reported reduced sleep disturbance following reduction mammaplasty, which has widespread health benefits.

Improvement in Oncologic Surveillance

After reduction mammaplasty, women found it easier to perform breast self-examinations, which theoretically could lead to earlier detection of breast cancer.[13] Reduction mammaplasty can be oncologically beneficial because premalignant or susceptible cells could potentially be removed[14]; this is evidenced by the occasional finding of occult breast carcinomas in breast reduction specimens.[15] Furthermore, a dense mammographic pattern, resulting from a high proportion of the breast occupied by mammary tissue, is associated with an increased breast cancer risk.[16,17] In addition, several epidemiologic studies have observed a substantial reduction in breast cancer risk in women who have had reduction mammaplasty.[18,19] In fact, one study

Table 1. Effects of Reduction Mammaplasty on Physical Symptoms

Reference	No.	Follow-Up (days)	Symptom Evaluaton	Outcomes Measure	Outcome	Level of Evidence
Bendite-Klepetko et al., 2007[5]	50	NA	Degenerative changes in spine	MRI	Patients with symptomatic macromastia have degenerative changes in their spine	III
Ducic et al., 2010[6]	84	968	Headache in patients with macromastia	10-point visual analogue scale	≥50% preoperative headaches resolved; statistically significant headache reduction	IIB
Foreman et al., 2009[7]	11	90	Lower back compressive forces; Functional Rating Index	Inverse dynamic evaluation	35% reduction postoperative low compressive back force; postoperative decrease in disability; 76% improvement in postoperative Functional Rating Index	IIB
Friere et al., 2007[8]	92	180	Functional capacity, pain	Visual analogue scale	Patients undergoing breast reduction had decreased back, shoulder, and neck pain frequency	IIB
				Stanford Health Assessment Questionnaire	Functional capacity improved in group that underwent reduction mammaplasty	
Starley et al., 1998[9]	19	60	Lung function	Pulmonary Function Testing Questionnaire	Significant improvement of PEFR, PIFR, FVC; improved exercise tolerance; reduced sleep disturbance; reduced breathing difficulty	IIB
Chao et al., 2002[10]	55	180	Disability	Lumbar Spine Outcome Assessment Instrument	Significantly improved postoperative disability scores	IIB
			Muscle strength	Kendall's Standardized Muscle Grading Scale	Significant improvement of rhomboid, middle and lower trapezius muscles	
			Postural evaluation	Harrison's Objective Clinical Measurements	Improved head translation and cranial rotation	
Chahraoui et al., 2006[11]	20	120	Sleep quality	General Health Questionnaire	Improvement in sleep quality	III

NA, not applicable; MRI, magnetic resonance imaging; PEFR, peak expiratory flow rate; PIFR, peak inspiratory flow rate; FVC, forced vital capacity.

even proposes reduction mammaplasty as a potential alternative to prophylactic mastectomy in high-risk women.[20]

Effect on Weight and Eating Behaviors

Table 2 illustrates studies that were evaluated in the literature with regard to the effect of breast reduction on weight, exercise practices, and eating behavior.[13,21–27]

The Obesity Myth

Thoma et al. found an improvement in health-related quality of life regardless of body mass index following reduction mammaplasty.[28] They found that this improvement translates into an expected lifetime gain of 5.32 quality-adjusted life-years using Health Utilities Index Mark evaluation. This study challenges the idea that women should be denied coverage because of their weight. Along these lines, many third-party payers suggest that obesity predisposes women to increased postoperative complications. Many studies report that, although overall complications increase with elevated body mass index, the majority of these complications are minor and do not affect the overall aesthetic outcome.[23,24,27] Although most insurance carriers mandate a certain reduction in grams for coverage of reduction mammaplasty, Spector and colleagues challenged this by noting a significant reduction in physical symptoms and improved quality of life regardless of the amount of tissue removed.[29] Several others have concluded that physical symptom improvement after breast reduction is not dependent on preoperative weight loss.[30–32]

Improvement in Exercise Practices

Macromastia often makes exercise difficult, and reduction mammaplasty has been shown to improve postoperative exercise practices. Boschert and colleagues found a significant increase in scheduled exercise time postoperatively.[26] Another study found that 100 percent of women found exercising easier and were able to participate in rigorous exercise postoperatively.[13] Recently, reduction mammaplasty was suggested to be a stimulus for weight loss in motivated women.[25] Women who viewed breast reduction surgery as a motivation for future weight loss had significant weight loss and dress size reduction, and exercised more. Weight loss and reduction mammaplasty are clearly linked in a positive feedback–type mechanism. Women with smaller breasts after reduction mammaplasty generally have improved self-esteem and are more likely to be comfortable in social situations involving exercise. This

Table 2. Effects of Reduction Mammaplasty on Exercise, Weight, and Eating Behaviors

Reference	No.	Follow-Up (yr)	Outcomes Measure	Effect on Weight	Level of Evidence
Kriepe et al., 1997[21]	5	4	Retrospective personal interviews	Bulimia improvement	III
Losee et al., 2004[22]	4	10	Eating Attitudes Test	Complete resolution of bulimia in all four patients following reduction mammaplasty	IIB
Shah et al., 2010[23]	306	5	Retrospective review of postoperative complication stratified by BMI	Elevated BMI has higher rate of minor complications but no effect on aesthetic outcome; authors caution the use of target BMI as exclusion criterion	III
Wagner and Alfonso, 2005[24]	186	NA	Retrospective chart review	No relationship between obesity of any degree and the results of reduction mammaplasty	III
Singh et al., 2010[25]	41	1–6	Questionnaire	Motivated patients exhibited significant weight loss and dress size reduction and exercised more after reduction mammaplasty; these patients had improved self-image and were more likely to participate in sexual activity	IIB
Boschert et al., 1996[26]	72	5	Questionnaire	No significant weight change over time; significant increase in scheduled exercise time	III
Brown et al., 2008[13]	141	NA	Questionnaire	22% improvement in exercise practices after breast reduction	IIB
Roehl et al., 2008[27]	179	1–10	Retrospective chart review	No significant correlation between size of breast tissue removed, age, and/or BMI and postoperative complications	III

BMI, body mass index; NA, not applicable.

translates into greater physical activity and self-esteem, which could mean greater weight loss. Considered together, these studies suggest that obesity should not be justification for discrimination against surgical treatment of macromastia and that, in fact, surgery may actually promote weight loss following reduction mammaplasty.

Improvement of Eating Disorders

Macromastia is implicated as a factor contributing to eating disorders caused by a disproportionate upper body. Women may overeat in an attempt to camouflage their large breasts or may restrict their eating to try to decrease their breast size; these behaviors may lead to eating disorders such as bulimia nervosa.[33] Losee et al. described breast reduction as an effective therapy for macromastia in four young women with bulimia.[22] These women described the onset of their eating disorders after the development of macromastia. Postoperatively, all women reported improved body satisfaction and eating behaviors as measured by the Eating Attitudes Test, an established validated tool in the evaluation of patients with eating disorders. In fact, 10 years after surgery, all patients had complete resolution of bulimia nervosa. They suggest that the presence of an eating disorder should not necessarily exclude patients from reduction mammaplasty. Kreipe et al. reported similar findings in five young women with bulimia and macromastia who had significant physical and emotional symptom reduction after reduction mammaplasty.[21]

Psychological Improvements

Table 3 highlights the relevant literature review of the effect of reduction mammaplasty on women's psychological improvement.[11,34–37]

Improvement of Anxiety and Depression

Nearly one-third of women presenting with macromastia have clinical evidence of anxiety or depression.[5,38] Increasing breast mass has been specifically linked to the development of depressive symptoms.[5] Reduction mammaplasty has been shown to improve depression and anxiety.[11,38] In one study, women were evaluated with Spielberger's State-Trait Anxiety Inventory, a frequently used anxiety self-evaluation scale that evaluates anxiety trait and state anxiety.[11] Both the level of situation-related (state) and personality-related (trait) anxiety fell significantly after breast reduction. The authors postulate that this change is related to the reorganization of psychological balance related to the positive change in body image after surgery. Another group used the Beck Depression Inventory to assess levels of anxiety and depression among women preoperatively and

Table 3. Effects of Reduction Mammaplasty on Psyche

Reference	Follow-Up (mo)	No.	Symptom Evaluation	Outcomes Measure	Outcome	Level of Evidence
Turhan-Haktanir et al., 2010[34]	6	24	Temperament, character	TCI, Rosenberg Self-Esteem Scale	Women with large breasts have lower persistence (a temperament characteristic); significant increase in self-esteem following reduction mammaplasty	III
Saariniemi et al., 2009[35]	6	82	Depression, self-esteem	RBDI	Significantly less depression and improved self-esteem was seen after reduction mammaplasty compared to patients treated with conservative treatment	IIB
Romeo et al., 2010[36]	18–24	57	Psychosexuality	FSFI, SF-36	SF-36 and FSFI showed a strong distinct correlation postoperatively	III
Mello et al., 2010[37]	4	30	Quality of life	SF-36 quality-of-life inventory	Significant improvement in nearly all aspects of quality of life	III
				Rosenberg Self-Esteem Scale	Significant improvement in self-esteem after breast reduction	
Chahraoui et al., 2006[11]	4	20	Anxiety	State-Trait Anxiety Inventory	Significant improvement in state and trait anxiety	

TCI, Temperament and Character Inventory; RBDI, Modification of Beck Depression Inventory; FSFI, Female Sexual Function Index; SF-36, 36-Item Short-Form Health Survey.

postoperatively and compared this group to women who did not undergo breast reduction.[35] They found a significant reduction in depression and anxiety. Moreover, the positive effect that reduction mammaplasty has on decreasing anxiety and depression appears to be longstanding. One study followed women for 5 years postoperatively and found a sustained improvement in anxiety and depression.[39]

Improvement in Self-Esteem

Breast reduction improves women's self-esteem. Using the Rosenberg Self-Esteem Scale, one study found a significant improvement of self-esteem at 1 and 4 months after reduction mammaplasty.[37] This is particularly interesting because, at 1 month postoperatively, there may still be discomfort and considerable adaptation of the breasts with regard to swelling and scarring. Numerous other studies have similarly used the Rosenberg Self-Esteem Scale to specifically evaluate self-esteem following reduction mammaplasty and have shown an improvement in self-esteem postoperatively.[40–42] Another group studied the effect of reduction mammaplasty on temperament and self-esteem. They found that women with large breasts have a lower level of the persistence temperament characteristic and that this characteristic and self-esteem improves after breast reduction.[34]

Improvement in Quality of Life

Reduction mammaplasty improves women's quality of life substantially. One evaluation used the 36-Item Short-Form Health Survey quality-of-life inventory to evaluate women at 30 and 120 days after breast reduction and found statistically significant improvement at both time points.[37] Kerrigan et al. introduced the concept of utilities, or preference-based measures of health-related quality of life, with regard to evaluating women undergoing reduction mammaplasty. They used a standard gamble technique and a table, which includes different iterations of percentages of the change of life without macromastia symptoms and the chance of death from surgery.[40] In this elegant study, they highlight the importance of disease-specific evaluation of quality of life, which was not previously described. They offer specific recommendations for standardized self-assessment tools to evaluate women undergoing breast reduction surgery. In particular, they quantify the effect of macromastia on quality of life as a standard gamble utility of 0.73 to 0.93, which is similar to that of moderate angina (0.90) and arthritis (0.78). These measures are based on a bimodal system of evaluation, where 0 represents death and 1 represents perfect health. As such, these authors advocate using a self-administered, paper-based table as a valid measure of utility for breast hypertrophy. Shakespeare and Postle used the Rosenberg Self-Esteem Scale to prospectively evaluate 60 women who had reduction mammaplasty.[41] Like others, they conclude that the improvement of pain and discomfort from macromastia following breast reduction leads to a sustained positive effect on physical activity and general health, self-confidence, and relationships.[41,42] Other studies used the 36-Item Short-Form Health Survey, a health-related quality-of-life evaluation, and the Brief Symptom Inventory, which measures psychological symptoms, to assess women undergoing reduction mammaplasty.[34] They compared patients' responses to age-matched controls preoperatively and postoperatively and found that responses between the two groups were similar 9 months after surgery. Others observed the positive effect that breast reduction has on women's quality of life with regard to femininity, wholeness, ease of making social contacts, and being less bothered in social or intimate situations.[43]

Improvement in Psychosexual Function

It has been reported that up to 80 percent of women with macromastia have sexual difficulties.[38] These women dislike having their partners touch their breasts because of embarrassment relating to the size of their breasts. Women appear to have improved psychosexual function after reduction mammaplasty. One study used the Female Sexual Function Index (a validated questionnaire for assessing female sexual function) and the 36-Item Short-Form Health Survey (for assessing quality of life) to evaluate 55 women after reduction mammaplasty.[36] They found a strong correlation between elevated 36-Item Short-Form Health Survey scores on the Female Sexual Function Index. This is not a surprising conclusion, because one would assume that an enhanced quality of life could positively affect a women's sexual function. Another evaluation of 80 women after reduction mammaplasty found significant improvement in confidence during intimate situations.[44] They found a significant correlation between operative and sexual satisfaction. As one might expect, there appears to be an association between diminished nipple sensation and sexual satisfaction after reduction mammaplasty. Women are more willing to engage in sexual activities and are more comfortable without their clothes on after reduction mammaplasty.[25]

Aesthetic Evaluation

Although reduction mammaplasty is not considered an aesthetic procedure, and physical and

psychological benefits have been demonstrated, aesthetic outcome is also important and often a point of dissatisfaction. Specific evaluation of aesthetic improvement following reduction mammaplasty was reviewed. Table 4 lists the relevant literature related to this topic.[45–47]

Aesthetic Improvement

Because reduction mammaplasty causes a significant change in body shape, patient satisfaction is dependent on achieving aesthetic goals. Borkenhagen et al. described the Digital-Body-Photo-Test to assess body image changes after reduction mammaplasty.[45] In this test, a subject's own body parts are presented to the patient and she is asked to indicate how satisfied she is with that particular area using different colors. They showed that women had higher satisfaction rates with nearly all parts of their bodies following reduction mammaplasty. Another study used an extensive questionnaire to evaluate patient satisfaction with body harmony, breast shape, symmetry, and the nipple-areola complex.[47] In the same study, four consultant surgeons were then blindly asked to assess postoperative photographs of patients' breasts. Patients and surgeon responses were scored. They showed that women were satisfied with the aesthetic appearance of their breasts; notably, the surgeons were more critical of the aesthetic outcomes than the patients. Since Penn's original description of the ideal nipple-to–sternal notch distance, many authors have used these specifications to denote an aesthetic breast.[48] As such, one study measured the nipple-to–sternal notch and nipple-to–inframammary fold distances and patient and blinded surgeon subjective evaluations.[46] The mean nipple-to–sternal notch distance was 21.6 cm and the mean nipple-to–inframammary fold distance was 7.5 cm, which is in accord with standard ideal measurements. Patient and surgeon aesthetic evaluations were high as well. It should be noted that there are few studies in the literature that formally address aesthetic evaluation following reduction mammaplasty.

Table 4. Effects of Reduction Mammaplasty on Appearance

Reference	No.	Follow-Up (mo)	Symptom Evaluation	Outcomes Measure	Outcome	Level of Evidence
Borkenhagen et al., 2007[45]	40	NA	Body image	Digital-Body-Photo-Test	Women reported higher satisfaction rates with nearly all parts of their body following reduction mammaplasty	III
Eggert et al., 2009[46]	65	6	Symmetry appearance	N-N and N-IMF distances; plastic surgeon evaluation of postoperative photographs; patient questionnaires	Mean N-N distance, 21.6 cm; mean N-IMF distance, 7.5 cm; patient satisfaction rates correlated with plastic surgeons' aesthetic evaluation scores; mean satisfaction score, 6.4 (scale 1–7)	III
Godwin et al., 1998[47]	34	12	Appearance	Questionnaire	Overall satisfaction with aesthetic outcome	III

NA, not applicable; N-N, nipple-to–sternal notch; N-IMF, nipple-to–inframammary fold.

DISCUSSION

It is clear that breast reductions do more than simply reduce the size of a woman's breasts, which is why reduction mammaplasty has such high patient satisfaction rates.[49] The positive physical and emotional benefits of reduction mammaplasty are unambiguous. There is an obvious and predictable interplay of positive feedback on the improvement of various dimensions of a women's life fol-

lowing breast reduction. The strength of this systematic review lies in its unique completeness with regard to the overall benefits of breast reduction on the physical, weight-related, and psychological effects of macromastia. When considered together, this information is a powerful tool for the plastic surgeon to have when addressing these patients in the preoperative and postoperative process. Insurance companies will often require women who seek reduction mammaplasty to document alternative therapies such as physical therapy, weight loss, or pain medication before even being referred to a plastic surgeon. These obstacles may in fact worsen the negative psychological impact of macromastia. Insurance companies and third-party payers should be aware of the tremendous benefits that breast reduction offers women with macromastia. Cost analysis of conservative treatment of macromastia is unfavorable and economically inefficient.[50] Numerous studies have concluded that reduction mammaplasty leads to a statistically significant improvement in health-related quality of life at a reasonable cost per quality-adjusted life-year.[51,52]

Part of the problem with any assessment tools is uniformity of reporting. It may be beneficial to plastic surgeons and patients alike to standardize outcomes reporting. Such standardization could not only assist in improving insurance coverage for reduction mammaplasty but might also facilitate comparisons between different techniques in breast reduction and in the evaluation of complications.

It is clear from our review that women have improved physical functioning after reduction mammaplasty. They have improved pain, skeletal stability, and lung function; they sleep better; and they have fewer headaches. At the same time, reduction mammaplasty is a stimulus for weight loss, exercise, and healthy eating behaviors. Women also have improved self-esteem, less anxiety and depression, and improved quality of life. Although the evaluations are few, it appears that most women are pleased with the aesthetic quality of their breasts after reduction mammaplasty.

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The Breast Journal

ORIGINAL ARTICLE

Quality of Life Following Symptomatic Macromastia Surgery: Short- and Long-term Evaluation

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■ **Abstract:** Mammary hypertrophy or macromastia can cause a wide range of symptoms (physical, psychosomatic or behavioral), which affect patients' quality of life. Breast reduction can, in most of the cases, solve the problem. However, certain factors could have a negative effect on the outcome of surgery. The aims of this study were to discover the degree of patient satisfaction (short- and long-term) and to evaluate results of reduction mammoplasty, and also to ascertain which factors may have a negative role on the effectiveness of breast reduction surgery. We carried out a prospective and longitudinal study of 121 patients who underwent breast reduction surgery. Quality of life, outcome of surgery (complications and sequelae) and degree of patient satisfaction were evaluated at 1 month and at 1 year after reduction mammoplasty. Mean patient age was 40.71 (SD = 12.02). Among them, 35.5% were overweight, 44.6% were obese and 34.7% were smokers. The most common symptom was pain. The mean amount of resected breast tissue was 1785 g (SD = 876). A total of 27.3% of the patients suffered complications and 30.60% suffered sequelae. Our results show an improvement in symptoms ($p < 0.001$) and quality of life ($p < 0.001$ to $p = 0.002$) 1 month after and 1 year after breast reduction compared with the preoperative situation. Neither age, body mass index, smoking habit nor the amount of tissue removed had a negative effect on the results of surgery. One year after surgery, the majority of patients were satisfied with the outcome (96.6%), they would recommend it to others (96.6%), and they would undergo surgery a second time (95.8%). Conclusions: Breast reduction is highly efficient in resolving symptoms and in improving quality of life. It leads to a high level of short- and long-term satisfaction irrespective of each patient's individual characteristics. ■

Key Words: breast reduction, macromastia, quality of life, reduction mammoplasty, satisfaction

Mammary hypertrophy is defined as an excessive, diffuse and in some cases, discapacitating development of one, or both breasts with no pathologic process nor underlying illness. There is no known etiology of macromastia and it is thought to be a multifactorial process. While on many occasions macromastia does not produce physical or psychological alterations, it can, however, lead to many clinical pictures. Symptomatic macromastia is defined as a symptomatic complex which is different in each individual woman. It is characterized by physical, psychosomatic, and behavioral symptoms induced, in most cases, by mammary hypertrophy and resolved, in most cases, by breast reduction surgery (1).

Sometimes, it is difficult to distinguish between a normal breast and a hypertrophic breast since diagnosis of macromastia is often lacking in objective evidence. It must therefore be based first, on the evaluation of the signs and symptoms presented by the patient and, second, on the exploration carried out by the doctor her/himself so as to ascertain the degree of severity and intensity.

Symptoms related to macromastia are chronic pain (neck, shoulders, dorsal column, breasts and superior extremities, etc.), fatigue, difficulty in carrying out daily activities, tingling in the hands, intertrigo in the upper layers of the skin, skin grooves caused by the constant pressure of the bra straps, and on occasions, headaches. The differences in symptoms perceived between populations, patient age or social groups are significant (2).

Macromastia can even have a negative mechanical effect on the fastening and balancing systems of the backbone since the excess of weight in the front part of the chest can cause a redistribution of the forces which hold the torso upright and in the correct position (3).

Macromastia is associated with a more sedentary lifestyle and with difficulty to exercise. Moreover, it

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How Does Volume of Resection Relate to Symptom Relief for Reduction Mammaplasty Patients?

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Background: Reduction mammaplasty surgery is well known to produce improvement in a wide range of symptoms associated with macromastia. Health care insurers frequently stipulate a minimum resection volume to qualify for coverage, limiting access to surgery for many. The authors aimed to identify whether small volume resections do produce symptomatic improvement, comparing preoperative and postoperative experience of symptoms across a range of tissue resection volumes.

Methods: Reduction mammaplasty patients were given a custom-designed questionnaire at routine postoperative follow-up appointments, asking them to rate their preoperative and postoperative experience of 9 symptoms related to macromastia. Results were compiled and analyzed alongside data from patient case notes. Of 661 patients identified as being eligible for inclusion in the study, 410 had sufficiently complete data to proceed to statistical analysis. Patients were divided into 6 groups based on volume of breast tissue resected. A Schnur sliding scale percentile was also calculated for all patients. Statistical analysis of preoperative symptom prevalence and postoperative symptom change was carried out. Further analysis to examine for evidence of trend in symptom improvement across groups was implemented using the Jonckheere-Terpstra test for ordered alternatives.

Results: Patients who go on to have larger volumes of breast tissue resected were found to experience back pain, shoulder grooves, breast pain, rashes under the breast, exercise intolerance, and poor posture more frequently than those who go on to have smaller resections ($P < 0.0005$ for all). However, across the range of resection volumes, preoperatively symptomatic patients experienced significant improvement in several symptoms. Results suggested that a larger resection volume may correspond with greater improvement in back pain, neck pain, and poor posture.

Conclusions: We found that reduction mammaplasty has a positive impact on a range of symptoms, even with lower volume resections and regardless of body surface area–calculated adjustments. This adds further weight to the argument that patients should not be denied access to the surgery based on arbitrary volume restrictions. We advocate freedom for the surgeon to make a decision on potential benefits of surgery based around the needs of each individual patient.

Key Words: breast hypertrophy, breast reduction, reduction mammaplasty, symptom, symptoms, outcomes, patient satisfaction, symptom improvement, insurance, Schnur sliding scale

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A wide body of evidence proves a link between macromastia and numerous symptoms, as well as demonstrating that reduction mammaplasty is beneficial in ameliorating many of them.[1–4] However, health care insurance providers in the United States and Canada often stipulate a minimum amount of breast tissue to be resected to qualify for coverage, with many now using a body surface area (BSA)–adjusted value based on the sliding scale described by Schnur et al.[5] Despite this, the literature to date shows no evidence that larger volume resections contribute to greater symptom improvement.[6,7] Furthermore, Kerrigan et al[8] showed that in preoperative breast reduction candidates, no linear relationship between bra cup size and experience of breast-related symptoms exists. So far, there have been few publications focused on comparing amount of tissue resected with symptom-related outcomes. Spector et al[9] published a study in 2008 involving 188 women, provided with preoperative and postoperative questionnaires asking them to grade their experience of several symptoms. Patients were subsequently divided into 4 groups based on volume of tissue resected. He concluded that patients from all 4 groups experienced a similar degree of symptomatic improvement postoperatively. Wagner and Alfonso[7] investigated the impact of resection volume related to body mass index (BMI) in a study involving 186 patients, and found no significant relationship between either BMI or volume of resection on symptom improvement.

Although the literature published so far suggests that resection volume does not determine symptom improvement, few studies to date have examined this idea in patients undergoing "small" volume reductions. The study of Spector and Karp[10] of 59 patients found that symptomatic improvement occurred when less than 750-g total tissue was resected.

We studied a large number of reduction mammaplasty patients across a range of volume resections, including women who had less than 250-g tissue resected per breast. We aimed to identify whether a trend exists between increasing resection volume and symptom improvement, and whether there are differences in preoperative symptom prevalence and postoperative relief in patients undergoing the smallest volume resections.

METHOD

The authors identified patients who had undergone breast reduction surgery in the practice between December 1999 and December 2011. All of the patients were operated on by the senior author, and underwent reduction mammaplasty using a medial pedicle, vertical scar technique, as described by Hall-Findlay.[11] Patients who had undergone the procedure using a different pedicle or substantially modified technique were excluded from the study. In addition, all patients undergoing an additional procedure during the same anesthetic (or who were subsequently identified as having undergone an additional cosmetic procedure within the time to follow-up, with the exception of "dog-ear" revision) were excluded from the study.

Patients had been supplied with a custom-designed questionnaire at routine follow-up appointments, asking them to rate their experience of 9 symptoms before and after surgery, using a 4-point Likert scale: Back pain, neck pain, shoulder grooves, breast pain, rashes under the breasts, headache, exercise intolerance, and poor posture. These symptoms were chosen due to their perceived relationship with macromastia, and to encompass the physical, lifestyle, and psychological effects of living with large breasts. They were graded on a scale of 1 to 4 (1, none; 2, mild; 3, moderate; and 4, severe) (Fig. 1).

A total of 661 eligible patients were identified during the inclusion period. Of those patients, 151 were identified as having missing or substantially incomplete questionnaires, and were therefore excluded. Eleven further patients were excluded due to incomplete data, and a further 2 patients were excluded as their answers were not given in the correct format. Of the remaining 497 patients, 87 had completed their follow-up questionnaires within 30 days of surgery. These patients were also excluded from the study, as it was felt that such a short period to

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The Effectiveness of Surgical and Nonsurgical Interventions in Relieving the Symptoms of Macromastia

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In this report, the authors evaluate the effectiveness of breast reduction in alleviating the symptoms of macromastia by comparing baseline and postoperative health status using a series of well-validated self-report instruments. The study had a prospective design with a surgical intervention group and two control groups: a hypertrophy control group with bra cup sizes D or larger and a normal control group with bra cup sizes less than D. The effectiveness of nonsurgical interventions in relieving the symptoms of macromastia was also evaluated, both in the operative subjects and in the control groups.

Surgical candidates and controls completed a self-administered baseline survey that consisted of the following validated and standardized instruments commonly used to evaluate outcomes: SF-36, EuroQol, Multidimensional Body-Self Relations Questionnaire (MBSRQ), and the McGill Pain Questionnaire (MPQ). A specially designed and validated instrument, the Breast-Related Symptoms (BRS), was also used. There were also questions about prior nonsurgical treatments, comorbid conditions, bra size, and a physical assessment. Additional information obtained on the operative subjects included surgical procedure data, resection weight, and complications. Approximately 6 to 9 months postoperatively, surgical subjects completed the same questionnaire as described above, and a final physical assessment was performed.

The cohort included 179 operative subjects with matched preoperative and postoperative data sets, 96 normal controls and 88 hypertrophy controls. The women were predominantly Caucasian, middle-aged, well educated, and employed. Fifty percent of the operative subjects reported breast-related pain all or most of the time in the upper back, shoulders, neck, and lower back preoperatively compared with less than 10 percent postoperatively. Operative subjects and hypertrophy controls tried a number of conservative treatments, including weight loss, but none provided adequate permanent relief. Compared with population norms, the preoperative subjects had significantly lower scores ($p < 0.05$) in all eight health domains of the SF-36, and in the mental and physical component summary scores. After surgery, the operative subjects had higher means (better health) than national norms in seven of the eight domains and improved significantly from presurgical means in all eight domains ($p < 0.05$). Before surgery, the operative subjects reported high levels of pain with a Pain Rating Index (PRI) score from the MPQ of 26.6. After surgery, pain was significantly lower with a mean PRI score of 11.7, similar to that of our controls (mean PRI score, 11.2). Regression analysis was used to control for covariate effects on the main study outcomes. Among the operative subjects, benefits from breast reduction were not associated with body weight, bra cup size, or weight of resection, with essentially all patients benefiting from surgery.

Breast hypertrophy has a significant impact on women's health status and quality of life as measured by validated and widely used self-report instruments including the SF-36, MPQ, and EuroQol. Pain is a significant symptom in this disease, and both pain and overall health status are markedly improved by breast reduction. In this population, conservative measures such as weight loss, physical therapy, special brassieres, and medications did not provide effective permanent relief of symptoms. (*Plast. Reconstr. Surg.* 109: 1556, 2002.)

Plastic surgeons have long observed that reducing breast mass can effectively alleviate the symptoms associated with macromastia. Unfortunately, denials of insurance coverage and policy exclusions for breast reduction are becoming increasingly common. What has prompted these changes? Perhaps insurers do not accept that symptomatic macromastia is a

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Complications Following Reduction Mammaplasty: A Review of 3538 Cases From the 2005-2010 NSQIP Data Sets

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Abstract

Background: Reduction mammaplasty is an established and effective technique to treat symptomatic macromastia. Variable rates of complications have been reported, and there is a continued need for better outcome assessment studies.

Objective: The authors investigate predictors of postoperative complications following reduction mammaplasty using the National Surgery Quality Improvement Program (NSQIP) data sets.

Methods: The 2005-2010 American College of Surgeons NSQIP databases were reviewed to identify primary encounters for reduction mammaplasty using *Current Procedural Terminology* code 19318. Two complication types were recorded: major complications (deep infection and return to operating room) and any complication (all surgical complications). Preoperative patient factors and comorbidities, as well as intraoperative variables, were assessed. A multivariate regression analysis was used to identify independent predictors of complications.

Results: A total of 3538 patients were identified with an average age of 43 years and body mass index of 31.6 kg/m^2. Most patients underwent outpatient surgery (80.5%) with an average operative time of 180 minutes. The incidence of overall surgical complications was 5.1%. The following factors were independently associated with any surgical complications: morbid obesity (odds ratio [OR], 2.1; $P < .001$), active smoking (OR, 1.7; $P < .001$), history of dyspnea (OR, 2.0; $P < .001$), and resident participation (OR, 1.8; $P = .01$). The incidence of major surgical complications was 2.1%. Factors associated with major complications included active smoking (OR, 2.7; $P < .001$), dyspnea (OR, 2.6; $P < .001$), resident participation (OR, 2.1; $P < .001$), and inpatient surgery (OR, 1.8; $P = .01$).

Conclusions: This study demonstrates overall incidence of complications in 1 in 20 patients and a 1 in 50 incidence of a major surgical complication. Noteworthy findings include the identification of morbid obesity as a significant predictor of overall morbidity and active smoking as a strong predictor of major surgical morbidity. These data can assist surgeons in preoperative counseling and enhance perioperative decision making.

Level of Evidence: 3

Keywords

breast reduction, outcomes, NSQIP, complications

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Reduction mammaplasty is one of the most common surgical procedures performed by plastic surgeons in the United States.[1] Symptomatic breast hypertrophy can cause significant musculoskeletal pathology as well as chronic dermatologic conditions, including intertriginous rash along the inframammary fold, leading to decreased quality of life.[2-5] Reduction mammaplasty has been shown to significantly improve symptoms and quality of life.[6,7] These symptomatic improvements are complemented by high and durable rates

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A Multi-Institutional Perspective of Complication Rates for Elective Nonreconstructive Breast Surgery: An Analysis of NSQIP Data From 2006 to 2010

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Abstract

Background: As elective nonreconstructive breast surgery increases in popularity, there is greater demand for accurate multi-institutional data on minor and major postoperative complications.

Objective: The authors utilized a multi-institutional database to compare 30-day morbidities and reoperation rates among the different types of elective nonreconstructive breast surgery.

Methods: Patients in the National Surgical Quality Improvement Program (NSQIP) participant use file who underwent elective nonreconstructive breast surgery between 2006 and 2010 were identified. Twenty defined morbidities were compared among mastopexy, reduction mammaplasty, and augmentation mammaplasty patients using analysis of variance and χ^2 tests for continuous variables and categorical variables, respectively. Logistic regression modeling was employed to identify preoperative risk factors for complications.

Results: Of the 3612 patients identified, 380 underwent mastopexy, 2507 underwent reduction mammaplasty, and 725 underwent augmentation mammaplasty. Complication rates were low in all cohorts, and patients undergoing augmentation mammaplasty had the lowest overall complication rate compared with mastopexy and reduction mammaplasty (1.24%, 2.37%, and 4.47%). Patients undergoing reduction mammaplasty had a modestly elevated incidence of overall morbidity, superficial surgical site infections, and wound disruptions ($P < .05$). Moreover, 30-day reoperation rates for mastopexy, reduction mammaplasty, and augmentation mammaplasty were low (1.58%, 2.07%, and 0.97%), as were the rates of life-threatening complications (0%, 0.16%, and 0%). One death was observed for all 3612 procedures (0.03%).

Conclusions: Elective breast surgery is a safe procedure with an extremely low incidence of life-threatening complications and mortality. Comprehensive data collated from the NSQIP initiative add to the literature, and the findings of this multi-institutional study may help further guide patient education and expectations on potentially deleterious outcomes.

Level of Evidence: 3

Keywords

elective breast surgery, mastopexy, reduction mammaplasty, augmentation mammaplasty, NSQIP, outcomes, cosmetic breast surgery, complications

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Mastopexy, augmentation mammaplasty, and reduction mammaplasty rank among the most frequently performed elective and/or cosmetic plastic surgery procedures in the United States each year. Despite the fact that over 550 000 of these procedures were performed in 2011,[1] the vast majority of the outcomes research regarding mastopexy, augmentation mammaplasty, and reduction mammaplasty has focused on reports from a single surgeon or single group's experience, which only offers a narrow view of the potential outcomes from these procedures.[2-23] Multicenter

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data present the results of large series of patients across diverse geographical regions, which helps to account for differences in surgical technique and gives a well-balanced view of the risk profiles of these procedures. However, there are currently limited multicenter data evaluating these potential outcomes. For example, the Tracking Operations and Outcomes for Plastic Surgeons (TOPS) initiative was developed specifically to monitor the quality of plastic surgery. However, data from this registry are self-reported and not subject to auditing, which can introduce bias.[24] Another multi-institutional database, CosmetAssure, provides analysis of complications from cosmetic procedures but only reports data on complications requiring an emergency room visit, hospitalization, or reoperation.[24,25]

More recently, the National Surgical Quality Improvement Program (NSQIP) was established with the purpose of improving the quality of surgical care. This registry prospectively collects validated data from over 200 medical institutions across the United States, resulting in a diverse population that allows for a broad and comprehensive analysis. Numerous studies have documented the program's success in decreasing morbidity and mortality rates, shortening length of stay, and improving patient satisfaction in the public and private sectors.[26-29]

To our knowledge, only 1 study to date has queried the NSQIP data set from a plastic surgery to date perspective.[30] Although the lack of breast surgery–specific variables captured by NSQIP has been highlighted, the unique data set captures numerous points that are relevant for outcomes research in plastic surgery. The objective of this study was to further characterize mastopexy, reduction mammaplasty, and augmentation mammaplasty outcomes using NSQIP data and to compare these with existing morbidity data to provide a more comprehensive description of the outcomes from a multi-institutional perspective.

METHODS

For the purposes of this study, breast reduction was considered a cosmetic procedure, although in clinical practice breast reduction often may meet the criteria to be considered a non-cosmetic operation. Notably, reduction volume data was not captured by the NSQIP database. A retrospective analysis was conducted using the NSQIP participant use files from 2006 to 2010. The data collection methods for NSQIP have been extensively described previously.[31,32] In brief, NSQIP prospectively collects comprehensive patient data, including demographics, preoperative comorbidities and laboratory values, intraoperative details, and postoperative outcomes, within 30 days of the primary operation. Patients are selected based on a systematic sampling cycle that rotates every 8 days to ensure a broad and representative sample of procedures is captured. To ensure accuracy, participating sites are audited, and surgical certified reviewers (SCR) are rigorously trained to extract patient information according to standardized definitions.

Patients undergoing nonreconstructive elective breast surgery were identified using the primary *Current Procedural Terminology* (*CPT*) codes for mastopexy (19316), reduction mammaplasty (19318), and augmentation mammaplasty (19325). Males and patients without sex information were excluded. Patients undergoing additional procedures were also excluded. The inclusion process for this study is outlined in Figure 1. The outcomes of interest were postoperative morbidity, mortality, and reoperation. Morbidities included the following: superficial surgical site infection (SSI), deep SSI, organ space SSI, wound disruption, pneumonia, unplanned reintubation, pulmonary emboli, ventilator dependence >48 hours, progressive renal insufficiency, acute renal failure, urinary tract infection, stroke, coma, cardiac arrest, myocardial infarction, bleeding requiring transfusions, deep venous thrombosis (DVT), sepsis, septic shock, and graft/prosthesis/flap failure. The standards for each complication were used, as defined in the NSQIP user guide.[32]

Descriptive statistics were calculated for the study population. Chi-square tests were used to analyze cohorts across categorical variables, and analysis of variance (ANOVA) tests were used for continuous variables. Pairwise *z* tests were performed to compare intercohort proportions. In addition, multivariate logistic regression modeling was used to identify potential risk factors for overall complication within 30 days. Preoperative variables that were included in the models were as follows: age, length of surgery, obesity (defined as a body mass index [BMI] >25), smoking within 1 year of the operation, diabetes mellitus, chemotherapy within 30 days, dyspnea, hypertension (defined as a persistent elevation of systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg or patients requiring antihypertensive medication at the time the patient is being considered for surgery), and chronic steroid use (defined as patients who required regular administration of oral or parenteral corticosteroid medications within 30 days prior to surgery for a chronic medical condition). A 2-tailed *P* value of less than .05 was considered significant for all analyses. All data analyses were performed using SPSS version 20.0 (SPSS, Inc, an IBM Company, Chicago, Illinois).

RESULTS

A total of 3612 patients were identified, of whom 380 underwent mastopexy, 2507 underwent reduction mammaplasty, and 725 underwent augmentation mammaplasty. The mean (SD) age of mastopexy, reduction, and augmentation patients was 46.7 (12.5) years, 42.2 (14.0) years, and 36.4 (10.9) years, respectively. Descriptive statistics for the study population are summarized in Table 1.

On review, 130 (3.60%) patients experienced ≥1 morbidity, and 1 (0.03%) patient died. Overall morbidity was low in all cohorts but modestly elevated in reduction mammaplasty patients (4.47%) as compared with the mastopexy and augmentation groups (Table 2). In particular, individual outcomes for superficial SSI and wound complications revealed a statistically significant elevation in the reduction mammaplasty cohort as compared with augmentation patients ($P < .05$; Table 2). The median

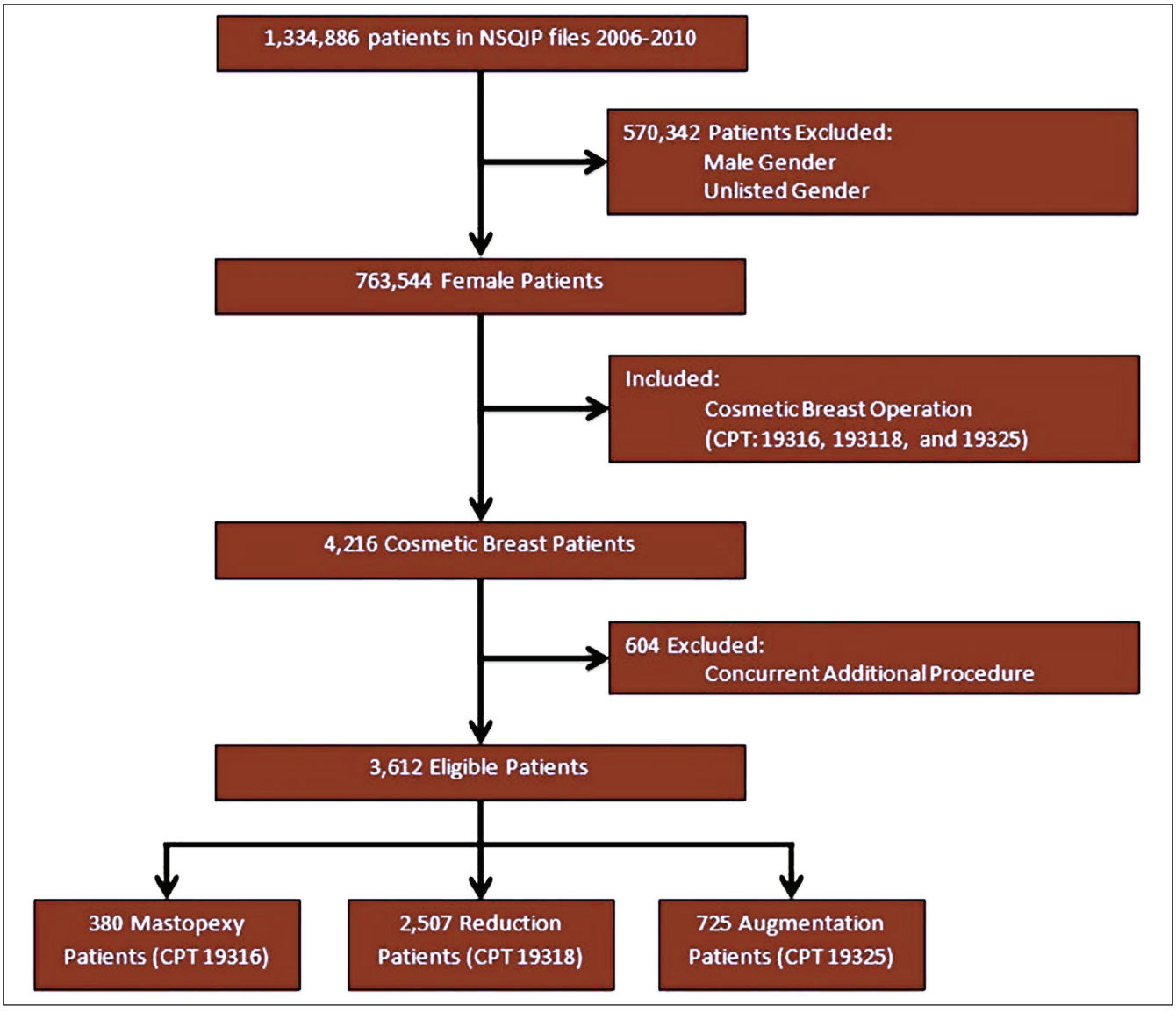

Figure 1. Study attrition diagram. CPT, *Current Procedural Terminology;* NSQIP, National Surgical Quality Improvement Program.

time to diagnosis for SSI occurred approximately 2 weeks after the index operation in all groups, ranging from 11 to 21 days. No incidences of pneumonia, pulmonary embolism, ventilator dependence, progressive and acute renal failure, coma, cardiac arrest, or septic shock were observed.

Life-threatening complications (pulmonary embolism, cardiac arrest, myocardial infarction, DVT, and sepsis or septic shock) were low for all groups and did not differ significantly among groups (Table 2). Overall, 65 (1.80%) patients returned to the operating room within 30 days of the index operation, but no statistical difference was observed in reoperation rates among procedure types (Table 2).

Obese patients demonstrated at least a 1.5-fold increase in overall morbidity rate in all 3 cohorts compared with nonobese patients; however, when included in the multivariate regression models, this association was deemed significant only for the augmentation mammaplasty cohort (Table 3). Diabetics also demonstrated elevated levels of morbidity, but this trend was not shown to be statistically significant in regression models. Patient age did not have a significant effect on adverse outcomes across all cohorts (Table 3). Length of surgery was associated with increased morbidity in the reduction and augmentation groups (P = .026 and P = .003, respectively). In addition, smoking was significantly associated with increased risk of complications in mastopexy patients (odds ratio [OR], 4.656), and dyspnea was associated with increased morbidity in the reduction cohort (OR, 2.37).

Table 1. Characterization of the Study Population

	Reduction Mammaplasty (n = 2507)	Mastopexy (n= 380)	Augmentation Mammaplasty (n = 725)
Age, y, mean (SD)	42.19 (13.97)	46.66 (12.53)	36.38 (10.87)
Race, No. (%)			
White	1536 (61.3)	280 (73.7)	506 (69.8)
African American	487 (19.4)	24 (6.3)	18 (2.5)
Other	484 (19.3)	76 (20.0)	201 (27.7)
Body mass index, mean (SD)	31.72 (6.76)	26.96 (7.12)	22.58 (3.80)

Table 2. Distribution of Postoperative Outcomes by Procedure Type

	Reduction Mammaplasty (n = 2507)			Mastopexy (n = 380)			Augmentation Mammaplasty (n = 725)			
	n	% Frequency	Median Day	n	% Frequency	Median Day	n	% Frequency	Median Day	*P* Value
Median day of initial hospital discharge			1			0			0	
Morbidity										
Superficial SSI	72_b	2.87	14.5	$5_{a,b}$	1.32	13	5_a	0.69	12	.001
Deep SSI	6_a	0.24	21	1_a	0.26	11	1_a	0.14	15	.863
Organ space SSI	1_a	0.04	21	0_a	0.00	—	0_a	—	—	.802
Wound disruption	23_b	0.92	20	$1_{a,b}$	0.26	23	0_a	—	—	.017
Pneumonia	0	—	—	0	—	—	0	—	—	—
Unplanned reintubation	1_a	0.04	1	0_a	—	—	0_a	—	—	.802
Pulmonary embolism	0	—	—	0	—	—	0	—	—	—
Ventilator >48 h	0	—	—	0	—	—	0	—	—	—
Progressive renal insufficiency	0	—	—	0	—	—	0	—	—	—
Acute renal failure	0	—	—	0	—	—	0	—	—	—
Urinary tract infection	4_a	0.16	8	0_a	—	—	3_a	0.41	8	.259
Stroke/CVA	0_a	—	—	0_a	—	—	1_a	0.14	2	.136
Coma >24 h	0	—	—	0	—	—	0	—	—	—
Cardiac arrest	0	—	—	0	—	—	0	—	—	—
Myocardial infarction	1_a	0.04	1	0_a	—	—	0_a	—	—	.802
Bleeding requiring transfusions	5_a	0.20	2	2_a	0.53	2	0_a	—	—	.167
Deep venous thrombosis	1_a	0.04	4	0_a	—	—	0_a	—	—	.802
Sepsis	2_a	0.08	6.5	0_a	—	—	0_a	—	—	.643
Septic shock	0	—	—	0	—	—	0	—	—	—
Graft/prosthesis/flap failure	3_a	0.12	11	0_a	—	—	0_a	—	—	.516
Total complications reported[a]	112_b	4.47	14	$9_{a,b}$	2.37	11	9_a	1.24	12	<.001
Reoperation	52_b	2.07	—	$6_{a,b}$	1.58	—	7_a	0.97	—	.133
Mortality	0_b	—	—	1_a	0.26	13	$0_{a,b}$	—	—	.014

Each subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other. CVA, cerebral vascular accident; SSI, surgical site infection. Dashes were entered in cases in which there was insufficient data to make the appropriate calculations.

[a]A single patient may have experienced more than 1 listed outcome.

Table 3. Association of Preoperative Variables With Postoperative Morbidity

	Reduction Mammaplasty (n = 2507)				Augmentation Mammaplasty (n = 725)				Mastopexy (n = 380)			
	Patients, No. (%)	Complications, No. (%)	Odds Ratio	*P* Value	Patients, No. (%)	Complications, No. (%)	Odds Ratio	*P* Value	Patients, No. (%)	Complications, No. (%)	Odds Ratio	*P* Value
Obesity	2156 (86.0)	103 (4.8)	1.54	.228	131 (18.1)	6 (4.6)	4.72	.041	209 (55.0)	6 (2.9)	1.555	.555
Smoking	300 (12.0)	17 (5.7)	1.31	.326	134 (18.5)	1 (0.7)	0.27	.308	49 (12.9)	3 (6.1)	4.656	.044
Diabetes	111 (4.4)	8 (7.2)	1.23	.611	11 (1.5)	1 (9.1)	3.10	.386	8 (2.1)	0 (0.0)	—	—
Chemotherapy	10 (0.4)	1 (10.0)	2.71	.351	1 (0.1)	0 (0.0)	—	—	11 (2.9)	1 (9.1)	4.554	.199
Dyspnea	70 (2.8)	8 (11.4)	2.37	.031	2 (0.3)	0 (0.0)	—	—	4 (1.1)	0 (0.0)	—	—
Hypertension	568 (22.7)	35 (6.2)	1.41	.157	36 (5.0)	3 (8.3)	2.40	.363	63 (16.6)	3 (4.8)	2.725	.525
Steroid use	23 (0.9)	2 (8.7)	1.79	.439	1 (0.1)	0 (0.0)	—	—	1 (0.3)	0 (0.0)	—	—
Age	—	—	1.00	.967	—	—	1.05	.192	—	—	1.017	.592
Operating time	—	—	1.00	.026	—	—	1.01	.003	—	—	1.002	.636

DISCUSSION

This study evaluates the 30-day morbidity profiles and risk factors of 3 elective breast surgical procedures: augmentation mammaplasty, reduction mammaplasty, and mastopexy. In general, these procedures are well tolerated by patients with overall complication rates lower than 5% for each of the 3 procedures. This is less than the complication rate suggested by the literature, with previous single-surgeon or institutional studies reporting a range of overall morbidity rates from 2% to 53% for reduction procedures,[2,13] 5% to changed to 38% for augmentation operations,[14,19] and 2% to 52% for mastopexy[20,23] (Table 4).

Existing studies are cited to provide a reference point for overall morbidity from these procedures, although a direct comparison of these results is difficult due to the focus on short-term outcomes by the NSQIP registry. Comparison data used in this study were found by searching the MEDLINE catalogue using PubMed. We included studies published within the past 15 years that focused on the outcomes of these single procedures and that reported complication information in sufficient detail. Studies attempting to validate new techniques or devices were excluded. We further restricted our analysis to studies that had a minimum of 100 patients for reduction and mastopexy procedures and 500 for augmentation procedures. The differences in observed complication rates in the literature are likely due to several factors. In particular, the severity and significance of complications reported varied dramatically between studies; some studies reported only severe complications that required intervention, whereas others included relatively minor adverse events such as changes in nipple sensation.[4,10,13] It is also important to note that the length of follow-up will affect the number of complications reported; the emphasis of the NSQIP registry is on short-term perioperative morbidity and risk factors, whereas many studies in the literature have extended follow-ups. Additional factors that influence the reporting of outcomes include the operating surgeon, implant type, and surgical technique. With such a large discrepancy in reported complication rates and a host of contributing factors, it can be difficult to extrapolate the results of these studies into practice. A more standardized approach to record and report plastic surgery–specific outcomes may yield more reliable data that can better inform prospective patients.

In the present study, 30-day morbidity and mortality rates were generally low for all procedures. However, reduction mammaplasty patients experienced marginally higher instances of overall morbidity (4.47%), superficial SSI (2.87%), and wound disruptions (0.92%) compared with mastopexy and augmentation patients. Although it is difficult to compare 3 different surgical procedures that, by nature, entail different risks, the differences in complication rates are likely due to the more extensive nature of reduction mammaplasties. In general, reduction mammaplasties entail more dissection and larger skin flaps than the other 2 procedures that were evaluated, which could lead to increased complication rates. Furthermore, the reduction mammaplasty cohort had a higher average BMI than the other groups studied, which has been documented to independently confer an additional risk of complications.[25,30,33-35] The volume of reduction may also be a significant factor in the development of adverse outcomes; however, this information was not captured by this database.

In the context of low overall morbidity, rates of life-threatening complications were extremely low, with rates

Table 4. Comparison of Reported Complication Rates by a Single Surgeon or Institution

Rate	n	Lead Author/Citation
Reduction		
2%	117	Moskovitz[2]
11%	371	Mandrekas[4]
14%	444	Stevens[5]
18%	153	Gulcelik[7]
20%	363	Schnur[8]
22%	799	Menke[9]
22%	338	Buenaventura[10]
23%	518	Scott[11]
53%	406	Davis[13]
21%		Mean
4%	2779	Present study
Augmentation		
5%	3002	Araco[14]
16%	1682	Huang[15]
21%	812	Codner[16]
23%	690	Tebbetts[17]
24%	749	Gabriel[18]
38%	619	Stutman[19]
21%		Mean
1%	839	Present study
Mastopexy		
2%	124	Flowers[20]
9%	150	Stevens[21]
21%	205	Caldeira[22]
52%	108	Rubin[23]
21%		Mean
2%	654	Present study

Table 5. Reduction Complication Rates From Multi-Institutional Studies

	Cunningham et al[38] (BRAVO)	Hanemann and Grotting[25] (CosmetAssure)	Present Study (NSQIP)
No. patients	179	904	2507
Wound infection, %	1.2	0.4	3.2
DVT/PE, %	—	—	<0.1
Reoperation, %	—	—	2.1
Overall morbidity, %	43.0	1.8	4.5

BRAVO, Breast Reduction Assessment: Values and Outcomes; DVT, deep venous thrombosis; NSQIP, National Surgical Quality Improvement Program; PE, pulmonary embolism.

of 0.00%, 0.16%, and 0.00% for mastopexy, reduction, and augmentation patients, respectively, validating the safety of these common elective breast procedures. In addition, 30-day reoperation rates were low for all procedure types, with mastopexy, reduction, and augmentation patients experiencing rates of 1.58%, 2.07%, and 0.97%, respectively, although the circumstances of reoperation were not captured by the NSQIP database. Prospective studies that record these details would improve our knowledge of reoperation and would also allow for improved patient counseling. With respect to the existing literature, observed reoperation rates in this analysis are relatively low, with a wide range of reported rates from 1.6% to 19.1%.[14,16,23,36] Similar to complication rates, discrepancies in reported reoperation rates may also be attributed to differences in surgeon, surgical technique, implant type, and follow-up length, all of which make it difficult to arrive at firm conclusions without additional comparative analysis.

Logistic modeling identified several comorbidities that were associated with an increased incidence of morbidity (Table 3). Patients with a BMI >25 were at an increased risk of complications in the augmentation cohort, which has been well documented in past studies.[25,30,33-35] Smoking was observed to confer an added risk of complications in the mastopexy cohort, which is in agreement with previous studies. It should be noted, however, that only a relatively small number of patients presented with some of these preoperative factors, which may limit the generalizability of these results. The length of surgery was also found to be associated with increased complications in both reduction and augmentation patients. Prior radiation treatment, which has been linked to adverse outcomes in previous cancer-based breast surgery studies, was not included in the regression models due to the low number of patients presenting with prior radiation.[30,37] This was undoubtedly due to the strict constraints on the timing of radiation prior to elective breast surgery by the NSQIP data collection protocols, which only capture radiotherapy occurring within 90 days prior to the operation and therefore limit the number of patients defined as having a positive history of radiation. In addition, NSQIP does not record the location of radiation, which would be useful for more in-depth analysis.

As mentioned previously, limited multi-institutional data assess the outcomes of cosmetic operations. Using TOPS data, Alderman et al[24] described an overall morbidity of 0.9% for augmentation mammaplasty procedures. This is slightly lower than the 1.24% found in this study

Table 6. Augmentation Complication Rates From Multi-Institutional Studies

	Alderman et al[24] (TOPS)	Alderman et al[24] (CosmetAssure)	Hanemann and Grotting[25] (CosmetAssure)	Henriksen et al[39] (DPB)	Hvilsom et al[40] (DPB)	Present Study (NSQIP)
No. patients	7310	3350	8929	1090	5373	725
Wound infection, %	0.3	0.1	0.2	0.9	1.5	0.8
DVT/PE, %	0.2	<0.01	—	—	—	0.0
Reoperation, %	—	—	—	24.2	4.8	1.0
Overall morbidity, %	0.9	0.8	1.7	26.3	16.7	1.2

DPB, Danish Registry for Plastic Surgery of the Breast; DVT, deep venous thrombosis; NSQIP, National Surgical Quality Improvement Program; PE, pulmonary embolism; TOPS, Tracking Operations and Outcomes for Plastic Surgeons.

Table 7. Mastopexy Complication Rates From Multi-Institutional Studies

	Hanemann et al[25] (CosmetAssure)	Present Study (NSQIP)
No. patients	1250	380
Wound infection, %	0.2	1.6
DVT/PE, %	—	0.0
Reoperation, %	—	1.6
Overall morbidity, %	1.8	2.4

DVT, deep venous thrombosis; NSQIP, National Surgical Quality Improvement Program; PE, pulmonary embolism.

(Tables 5-7), which could be due to the lower infection rate observed in the TOPS study as compared with the NSQIP data (0.3% vs 0.8%). Both of these observed rates suggest that augmentation mammaplasty procedures are well tolerated by patients. An additional multi-institutional study of reduction mammaplasty procedures, the Breast Reduction Assessment: Values and Outcomes (BRAVO) study, evaluated data from a multicentered, controlled evaluation of breast reduction complications. Data were prospectively collected for 15 months from 14 sites. The BRAVO study revealed an overall complication rate of 43%, which is dramatically higher than that reported from the NSQIP data (Tables 5-7). This may be due to the small sample size (n = 179) and inconsistent definitions and reporting of complications.[38]

In 1999, the Danish Registry for Plastic Surgery of the Breast (DPB) was established, marking the first nationwide prospective database that captures an array of cosmetic plastic surgery procedures. Data in the DPB are collected in a similar manner to the NSQIP data.[39,40] Compared with the results of this present study, analyses of the DPB have reported significantly higher rates of complications (Table 6), possibly due to the extended follow-up length (follow-up ranged from 0.1-8.7 years) and the design of the study, which included specific breast complications such as change in sensation and capsular contracture.[39,40] The NSQIP program was designed for multiple surgical specialties and therefore does not record all germane complications of breast procedures.

Use of the NSQIP database imparts a myriad of strengths to this study, including a large study population, validated and risk-adjusted data with standardized definitions, and reporting from over 200 medical institutions across the United States. In addition, these data are reliable and unbiased, with the fidelity of the data set having been previously tested.[28] Moreover, the data used in this study were derived from both inpatient and outpatient hospital settings, providing a perspective broad enough to incorporate many plastic surgery procedures. Using these data, we were able to analyze the short-term surgical complications for elective breast surgery, allowing for thorough evaluation of outcomes in the early postoperative period.

The main limitations of this study are the lack of procedure-specific outcomes reported by the NSQIP registry and the short length of follow-up. As a result, there may be an underreporting of complications in this study. Previous literature has suggested that plastic surgery–specific complications, such as capsular contracture, could be captured in future iterations of the registry.[30] These factors are not captured in this database and, along with cosmetic outcomes and patient satisfaction, should be studied in future efforts. In addition, a restructuring of the registry to increase its capture period from 30 days after the index operation to 90 days or even 1 year has been proposed, as many complications from plastic surgery can occur outside of the 30-day period.[30] These additions would allow for examination of longer-term outcomes that would increase the utility of NSQIP.

CONCLUSIONS

The prospective NSQIP database affords the ability to objectively track short-term morbidity, mortality, and reoperation rates of elective breast surgical procedures in both the inpatient and outpatient hospital environment. Extremely low mortality and morbidity rates—particularly life-threatening morbidities—validate the safety of these procedures when

performed in a hospital setting. Information garnered from the NSQIP data will be useful for informing patients and improving outcomes in our field.

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Disclaimer

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ASPS Clinical Practice Guideline Summary on Reduction Mammaplasty

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Summary: In May of 2011, the Executive Committee of the American Society of Plastic Surgeons approved an evidence-based guideline on reduction mammaplasty developed by the American Society of Plastic Surgeons Health Policy Committee. The guideline addresses six clinical questions: procedural efficacy as noted by relief of symptoms, resection weight, the impact of body mass index on surgical complications, use of prophylactic antibiotics, use of drains, and effect on quality of life. The evidence indicates that resection volume is not correlated directly to the degree of postoperative symptom relief. Increased breast resection weight may increase the risks of complication. The evidence is inconclusive on whether increased body mass index is associated with increased risk of complications. Perioperative antibiotics may reduce the risk of infection associated with reduction mammaplasty, and in standard reduction mammaplasty procedures without liposuction, the use of drains is not beneficial. Reduction mammaplasty has been shown to improve quality of life. (*Plast. Reconstr. Surg.* 130: 785, 2012.)

Symptomatic breast hypertrophy in women can have negative physical and psychosocial effects. As a consequence, symptomatic breast hypertrophy is recognized as a medical condition for which therapeutic intervention should be considered. Given the lack of a lasting and effective nonoperative treatment for this condition, symptomatic breast hypertrophy is most often managed by reduction mammaplasty.

Symptomatic breast hypertrophy is defined as a syndrome of persistent neck and shoulder pain with a tendency toward dorsal kyphosis; painful shoulder grooving from brassiere straps; chronic intertriginous rash of the inframammary fold; exacerbation of acne or hidradenitis suppurativa; and/or episodes of headache, backache, and upper extremity peripheral neuropathies caused by an increase in the volume and weight of breast tissue beyond normal proportions.[1-4] Some patients report difficulty with lifting or with participating in exercise and other physical activities. Sleeping may be difficult because of the weight of the breasts. Patients may also report low self-esteem, sexual harassment, and dissatisfaction with body image.[5-7] Although usually seen as symmetric involvement of both breasts, unilateral hypertrophy occasionally occurs. Breast hypertrophy may also become symptomatic after mastectomy of the opposite breast. Given these consequences, female symptomatic breast hypertrophy is recognized as a medical condition that can be effectively addressed surgically.

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Tobacco Smoking and Procedures - Vaping and Chew

Question: What is the HERC intent around vaping and smokeless tobacco in the new and revised guidelines about tobacco use and procedures?

Question source: Doug Luther, MD, CareOregon

Issue: At the October 2016 meeting, HERC approved a new ancillary guideline on tobacco smoking and elective procedures and made changes to other guidelines with smoking cessation requirements.

Since then, there have been questions about whether vaping and smokeless tobacco and whether or not they are included in these guidelines.

Current Prioritized List Status:

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Reproductive, cancer-related and diagnostic procedures are excluded from this guideline.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users (which is not a contraindication to elective surgery coverage). In patients using NRT the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing (well studied)
- Anabasine or anatabine testing

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,589

Bariatric surgery is included under the following criteria:

A) Age ≥ 18
B) The patient has
   1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE 2 DIABETES MELLITUS; OR
   2) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 589
C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from illicit drugs. Tobacco abstinence to be confirmed in active smokers by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with previous psychiatric illness must be stable for at least 6 months.
   2) Medical evaluation: (Conducted by OHP primary care provider)
      a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
      b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
      c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
   3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
      a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
      b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential

complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.

4) Dietician evaluation: (Conducted by licensed dietician)
   a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
   b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
   1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current certification by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing (MBSAQIP) certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 51,154,205,259,351,366,406,482,532,561

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date. Patients should be given access to appropriate smoking cessation therapy. Non-emergent spinal arthrodesis is defined as surgery for a patient with a lack of myelopathy or rapidly declining neurological exam.

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY

Line 288

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 288 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-10-CM J43.9) and all of the following:

A) BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
B) Stable with ≤20 mg prednisone (or equivalent) dose a day
C) Pulmonary function testing showing
    1) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
    2) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
    3) Residual volume (RV) ≥ 150% predicted post-bronchodilator
D) PCO 2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
E) PO 2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
F) Post-rehabilitation 6-min walk of ≥ 140 m
G) Non-smoking for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

GUIDELINE NOTE 159, SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION

Line 526

Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

Evidence Review:

Hartmann-Boyce, 2016

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010216.pub3/full

1. Cochrane systematic review of RCTs
2. 3 RCTs, only 2 included in the metaanalysis and 21 cohort studies

3. Two RCTs compared electronic cigarettes (EC) with placebo (non-nicotine) EC, with a combined sample size of 662 participants
4. Participants using an EC were more likely to have abstained from smoking for at least six months compared with participants using placebo EC (RR 2.29, 95% CI 1.05 to 4.96; placebo 4% versus EC 9%; 2 studies; 662 participants. GRADE: low). The one study that compared EC to nicotine patch found no significant difference in six-month abstinence rates, but the confidence intervals do not rule out a clinically important difference (RR 1.26, 95% CI 0.68 to 2.34; 584 participants. GRADE: very low).
5. Adverse effects are minor and most commonly mouth and throat irritation
6. Authors conclusions: There is evidence from two trials that ECs help smokers to stop smoking in the long term compared with placebo ECs (low confidence)

Malas, 2016

1. Systematic review of electronic cigarettes for smoking cessation
2. 62 references included in final assessment
3. Authors conclusions: While the majority of studies demonstrate a positive relationship between e-cigarette use and smoking cessation, the evidence remains inconclusive due to the low quality of the research published to date.

Khoudigian, 2016

1. Systematic review and meta-analysis of studies comparing e-cigarettes to other nicotine replacement therapies or placebo.
2. 5 studies were included
3. Use of nicotine e-cigarettes was associated with a statistically non-significant higher smoking cessation rate compared to placebo e-cigarettes (RR 2.02; 95% CI 0.97-4.22). Meta-analyses showed no difference in withdrawal symptoms or non-serious effects between the two groups.
4. Length of follow-up ranged from 1 day to 9 months
5. Authors conclusioins: Limited low-quality evidence of a non-statistically significant effect.

Pisinger, 2014

1. Systematic review of health effects of e-cigarettes, including animal studies
2. Studies found fine/ultrafine particles, harmfulmetals, carcinogenic tobaccospecific nitrosamines, volatile organic compounds, carcinogenic carbonyls (some in high but most in low/trace concentrations), cytotoxicity and changed gene expression. Of special concern are compounds not found in

conventional cigarettes, e.g. propylene glycol. Experimental studies found increased airway resistance after short-term exposure. Reports on short-term adverse events were often flawed by selection bias.

3. Authors conclusions: no firm conclusions can be drawn on the safety of ECs. However, they can hardly be considered harmless.

Taub, 2016

1. Narrative review
2. Authors without conflicts of interest
3. Nicotine is thought to impair flap survival due to vasoconstriction
4. Vaporized components could be toxic
5. Variability in nicotine dosing could add toxicity
6. Authors conclusions - “Based on our current best knowledge, it seems reasonable to advise plastic surgery candidates to cease e-cigarette use in a manner similar to what is advised with traditional nicotine inhalation compounds.”

Sorenson, 2012a

1. Systematic review and meta-analysis of RCTs and cohort studies comparing smokers and nonsmokers
2. 140 cohort studies including 479,150 patients
3. Smokers compared to nonsmokers - The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing.
4. Former smokers and patients who never smoked were compared in 24 studies including 47,764 patients, and former smokers and current smokers were compared in 20 studies including 40,629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications combined.
5. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).
6. Authors conclusions: Postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. Perioperative smoking cessation intervention reduces surgical site infections, but not other healing complications.

Sorenson, 2012b

1. Systematic review of pathophysiologic impacts of smoking, smoking cessation and NRT
2. 177 articles included
3. Damage from smoking is largely though tot occur via oxidative stress
4. Clinically, there is no evidence to suggest that nicotine administered as nicotine replacement drugs to abstinent smokers has a detrimental or beneficial effect on postoperative outcome of wound or tissue healing.

Walton, 2015

1. NIH electronic cigarette workshop to establish a research agenda
2. E cigarette aerosols do contain some toxic and carcinogenic compounds but are dramatically lower than combustible cigarettes
3. The majority of the e-liquid in e-cigarettes is comprised of propylene glycol and glycerol. These compounds have the designation, "Generally Regarded as Safe" as a food additive [but that GRAS does not apply to inhalation]. Additionally, propylene glycol is used in some asthma inhalers. For glycerol-containing solutions, one concern is that when heated they can produce acrolein, a compound shown to be harmful to lung function.Propylene glycol can cause airway irritation, eye inflammation, and nasal congestion, and some of these effects have been reported by users of e-cigarettes. The health effects of inhaling these constituents repeatedly throughout each day for years need to be evaluated.

On smokeless tobacco
CDC, 2016
https://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/health_effects/index.htm

1. Causes cancer of the mouth, esophagus, and pancreas
2. Is associated with diseases of the mouth
3. May increase the risk for death from heart disease and stroke

From Public Health

The question of whether to allow e-cigarette use as a perioperative strategy to assist patients with abstaining from tobacco use is a clinical management decision that is

beyond the scope of public health expertise. However, there are several public health factors that should be weighed in the decision. From the public health perspective, research shows that:

- The use of conventional cigarettes is related to wound healing problems and poorer outcomes in some types of surgery. Some surgical complications have been attributed to nicotine, so the use of e-cigarettes and smokeless tobacco would not eliminate this exposure. (1,4)

- The safety profile and long-term health effects of e-cigarettes are largely unknown. While most clinicians believe that e-cigarettes are safer than conventional cigarettes, they have been linked to a variety of adverse health effects, including pneumonia and congestive heart failure (1).

- The evidence for using e-cigarettes as a long-term strategy for cessation is weak. E-cigarette use has been shown to supplement and not replace conventional cigarette smoking long term, thereby creating "dual users" of conventional cigarettes and e-cigarettes (1, 2).

- Unlike other forms of nicotine replacement therapy (gum, patches, lozenges) the amount of nicotine in a vaping product like an e-cigarette is highly variable, which could have implications for surgery outcomes (1).

- Under the Indoor Clean Air Act, e-cigarette use is not allowed in hospitals in Oregon, so surgical patients cannot use them as a form of nicotine replacement during inpatient hospital stays (3).

1. Taub PJ & Matarasso A (2016) E-Cigarettes and Potential Implications for Plastic Surgery. *Plastic and Reconstructive Surgery*. *138(6*):1059e-1066e.

2. Bullen C, Howe C, Laugesen M, et al. (2013) Electronic cigarettes for smoking cessation: A randomized controlled trial. *Lancet*. 382: 1629-37.

3. Oregon's Indoor Clean Air Act-- About the Law. Accessed 2/2/2017 from: https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/SmokefreeWorkplaceLaw/Pages/thelaw.aspx

4. Nolan MB, Warner DO (2015) Safety and Efficacy of Nicotine Replacement Therapy in the Perioperative Period: A Narrative Review. *Mayo Clinic Proceedings.* 90(11):1553-1561.

Staff Summary

The impact of e-cigarettes on surgical outcomes is not understood. Preoperative smoking cessation with use of nicotine replacement is associated with improvements in surgical outcomes. E-cigarettes generally offer nicotine replacement, and with likely less harm than combustible cigarettes. While they should not be condoned as a first line smoking cessation therapy given the lack of evidence, at this point, they appear to be safer in the short term than combustible cigarettes and seem reasonable to allow in the context of elective procedures. However, at least one paper offers expert opinion that vaping should not be allowed similar to restrictions for other inhaled tobacco products.

Given both the unproven efficacy of e-cigarettes in smoking cessation, and lack of evidence on harms, their use would not be allowed for the surgical procedures that require full smoking cessation for 6 months (e.g. bariatric surgery, spinal fusion).

The counterargument to allowing vaping would be an inadvertent appearance of support for use of e-cigarettes as a smoking cessation tool, when the evidence is limited. Also, patients would not be allowed to vape in and around hospitals around the surgical period, unlike NRT or other pharmacologic therapy.

HERC Staff Recommendations:

OPTION 1 – Exclude e-cigarettes and smokeless tobacco from the elective surgery guideline (i.e. allow their use)

1. Modify the guidelines related to smoking cessation as follows

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Reproductive, cancer-related and diagnostic procedures are excluded from this guideline.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which ~~is not a~~ are not contraindications to elective surgery coverage). In patients using ~~NRT~~

nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing ~~(well studied)~~
- Anabasine or anatabine testing (NRT or vaping)

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

OPTION 2 Do not allow e-cigarettes or smokeless tobacco for 1 month prior to elective surgeries.

Modify the guidelines related to smoking cessation as follows

ANCILLARY GUIDELINE A4, TOBACCO USE, VAPING, ~~SMOKING CESSATION~~ AND ELECTIVE SURGICAL PROCEDURES

Cessation of tobacco and smoking (including traditional cigarettes, electronic nicotine delivery systems, and smokeless tobacco) ~~Smoking cessation~~ is required prior to elective surgical procedures for active ~~tobacco~~ users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from ~~smoking~~ use prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Reproductive, cancer-related and diagnostic procedures are excluded from this guideline.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users (which is not a contraindication to elective surgery coverage). In patients using NRT the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing (well studied)
- Anabasine or anatabine testing

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month

tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

2. Modify guideline notes 8, 100, 112, and 158 to clarify that use of any nicotine product including e-cigarettes or smokeless tobacco is not allowed within 6 months of the surgery.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,589

Bariatric surgery is included under the following criteria:

A) Age ≥ 18
B) The patient has
   1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE 2 DIABETES MELLITUS; OR
   2) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 589
C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in ~~active smokers~~ users by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with previous psychiatric illness must be stable for at least 6 months.
   2) Medical evaluation: (Conducted by OHP primary care provider)
      a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.

b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.

3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
   a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
   b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
4) Dietician evaluation: (Conducted by licensed dietician)
   a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
   b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
   1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current certification by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing (MBSAQIP) certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 51,154,205,259,351,366,406,482,532,561

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking and abstinent from any nicotine product for 6 months prior to the planned procedure, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date. Patients should be given access to appropriate smoking cessation therapy. Non-emergent spinal arthrodesis is defined as surgery for a patient with a lack of myelopathy or rapidly declining neurological exam.

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY

Line 288

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 288 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-10-CM J43.9) and all of the following:

A) BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
B) Stable with ≤20 mg prednisone (or equivalent) dose a day
C) Pulmonary function testing showing
    1) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
    2) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
    3) Residual volume (RV) ≥ 150% predicted post-bronchodilator
D) PO 2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
E) Post-rehabilitation 6-min walk of ≥ 140 m
F) Non-smoking and abstinence from any nicotine product for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

GUIDELINE NOTE 159, SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION

Line 526

Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking and abstinent from any nicotine product for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

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Review

Review

Electronic Cigarettes for Smoking Cessation: A Systematic Review

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Abstract

Background and Aims: Electronic cigarettes (e-cigarettes) have been steadily increasing in popularity among smokers, most of whom report using them to quit smoking. This study systematically reviews the current literature on the effectiveness of e-cigarettes as cessation aids.
Methods: We searched PubMed, MEDLINE, PsycINFO, CINAHL, ERIC, ROVER, Scopus, ISI Web of Science, Cochrane Library, the Ontario Tobacco Research Unit (OTRU) library catalogue, and various gray literature sources. We included all English-language, empirical quantitative and qualitative papers that investigated primary cessation outcomes (smoking abstinence or reduction) or secondary outcomes (abstinence-related withdrawal symptoms and craving reductions) and were published on or before February 1, 2016.
Results: Literature searches identified 2855 references. After removing duplicates and screening for eligibility, 62 relevant references were reviewed and appraised. In accordance with the GRADE system, the quality of the evidence in support of e-cigarettes' effectiveness in helping smokers quit was assessed as very low to low, and the evidence on smoking reduction was assessed as very low to moderate. The majority of included studies found that e-cigarettes, especially second-generation types, could alleviate smoking withdrawal symptoms and cravings in laboratory settings.
Conclusions: While the majority of studies demonstrate a positive relationship between e-cigarette use and smoking cessation, the evidence remains inconclusive due to the low quality of the research published to date. Well-designed randomized controlled trials and longitudinal, population studies are needed to further elucidate the role of e-cigarettes in smoking cessation.
Implications: This is the most comprehensive systematic evidence review to examine the relationship between e-cigarette use and smoking cessation among smokers. This review offers balanced and rigorous qualitative and quantitative analyses of published evidence on the effectiveness of e-cigarette use for smoking abstinence and reduction as well as important outcomes such as withdrawal symptoms and craving to smoke. While inconclusive due to low quality, overall the existing literature suggests e-cigarettes may be helpful for some smokers for quitting or reducing smoking. However, more carefully designed and scientifically sound studies are urgently needed to establish unequivocally the long-term cessation effects of e-cigarettes and to better understand of how and when e-cigarettes may be helpful.

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REVIEW

The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis

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Abstract
Objectives E-cigarettes are increasingly popular as smoking cessation aids. This review assessed the efficacy of e-cigarettes for smoking cessation as well as desire to smoke, withdrawal symptoms, and adverse events in adult smokers.
Methods A systematic review was conducted. Studies comparing e-cigarettes to other nicotine replacement therapies or placebo were included. Data were pooled using meta-analysis.
Results Of 569 articles, 5 were eligible. Study participants were more likely to stop smoking when using nicotine e-cigarettes (43/489, 9 %) versus placebo e-cigarettes (8/173, 5 %); however, this difference was not statistically significant (RR 2.02; 95 % CI 0.97, 4.22). The pooled effect estimates for the desire to smoke (RR −0.22; 95 % CI −0.80, 0.36), irritability (RR −0.03; 95% CI −0.38, 0.31), restlessness (RR −0.03; 95 % CI −0.42, 0.35), poor concentration (RR −0.01; 95 % CI −0.35, 0.32), depression (RR −0.01; 95 % CI −0.22, 0.20), hunger (RR −0.01; 95 % CI −0.32, 0.30), and average number of non-serious adverse events (RR −0.09; 95 % CI −0.28, 0.46) were not statistically significantly different. Only one study reported serious adverse events with no apparent association with e-cigarette use.
Conclusions Limited low-quality evidence of a non-statistically significant trend toward smoking cessation in adults using nicotine e-cigarettes exists compared with other therapies or placebo. Larger, high-quality studies are needed to inform policy decisions.

Keywords Meta-analysis · E-cigarettes · Smoking cessation · Withdrawal symptoms · Public health

Introduction

An estimated 1.2 billion people use tobacco worldwide (World Health Organization 2014). Tobacco-related deaths are one of the main causes of preventable early mortality, claiming 5 million lives annually (World Health Organization 2014). Smoking cessation is associated with significant health benefits, including reducing the risk of developing lung cancer, heart disease, and stroke (Polosa and Benowitz 2011). Despite the benefits of cessation and the desire of most smokers to quit, approximately 80 % of those who attempt to quit on their own relapse within the first month of abstinence, and only 3-5 % remain abstinent for 6 months or longer (Hughes et al. 2004).

The most common aids for smoking cessation are nicotine replacement therapies (NRTs), such as skin patches and chewing gums. However, they do not provide the additional sensory rituals that smokers seek (Caponnetto

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Review

A systematic review of health effects of electronic cigarettes

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Keywords:
Electronic cigarette
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ENDS
Electronic nicotine delivery system
Electronic nicotine delivery device

ABSTRACT

Objective: To provide a systematic review of the existing literature on health consequences of vaporing of electronic cigarettes (ECs).

Methods: Search in: PubMed, EMBASE and CINAHL. Inclusion criteria: Original publications describing a health-related topic, published before 14 August 2014. PRISMA recommendations were followed. We identified 1101 studies; 271 relevant after screening; 94 eligible.

Results: We included 76 studies investigating content of fluid/vapor of ECs, reports on adverse events and human and animal experimental studies. Serious methodological problems were identified. In 34% of the articles the authors had a conflict of interest. Studies found fine/ultrafine particles, harmful metals, carcinogenic tobacco-specific nitrosamines, volatile organic compounds, carcinogenic carbonyls (some in high but most in low/trace concentrations), cytotoxicity and changed gene expression. Of special concern are compounds not found in conventional cigarettes, e.g. propylene glycol. Experimental studies found increased airway resistance after short-term exposure. Reports on short-term adverse events were often flawed by selection bias.

Conclusions: Due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of ECs. However, they can hardly be considered harmless.

Contents

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Introduction

The electronic cigarette (EC), also called e-cigarette, e-cig, electronic vaping device, personal vaporizer or electronic nicotine delivery system (ENDS) has been on the market for a decade. ECs are marketed as safe products providing a sensation of traditional smoking without the harmful effects, delivering pure nicotine and releasing harmless water vapor that vanishes in seconds (Anon, 2014; Smoke, 2014). Puffing activates the battery-operated heating element in the atomizer and the liquid. The liquid consists of various combinations of propylene glycol, glycerin, nicotine, tobacco extracts, flavorants and/or adulterants which vaporize to an aerosol/vapor. The newer generations of ECs seem to be very efficient nicotine delivery systems (Etter and Bullen, 2011a; Wall et al., 1988). Almost all regular users use ECs with nicotine Etter and Bullen, 2011b.

In the beginning, ECs were primarily produced by small manufacturers in China and sold on the Internet without drawing major attention. In the last few years, major tobacco companies such as Lorillard, British American Tobacco, Altria, Reynolds and Imperial Tobacco have launched their own EC brands and are buying up existing ones. Marketing and sale has exploded and EC-shops and -lounges pop-up everywhere. For the first time in more than 40 years tobacco companies are back on TV with cigarette ads CNN Money, 2014. Industrial economists project that the ECs will surpass conventional cigarettes (CC) in about three decades, and the global EC market is expected to hit $10 billion by 2017 (Lopes, 2013; Stocks, 2013).

The epidemic spread of this new product raises great concern in some health and public health professionals sglanz, 2014 and great enthusiasm in others, who support the idea of "harm reduction" and see the EC as a long-awaited alternative to the conventional cigarette. Tobacco is the most deadly product on the market, and it is estimated that it will cause 1 billion deaths in the 21st century Eriksen et al., 2012.

Discussions concerning this new product are characterized by strong feelings and beliefs, as well as strong economic interests, making it very difficult to obtain unbiased information. There are many important issues concerning the EC, the most important being their long-term health effects.

The aim of this article is to give a systematic and critical review of the existing literature on the health consequences of vaping of ECs and discuss the implications of our findings for public health. Furthermore, as a first, we want to investigate how many of the published articles have a conflict of interest.

Objectives

We examined the published data to:

- Identify original publications on ECs which describe a health-related topic.
- Examine critically the design of the studies, the funding and other conflicts of interest and their influence on conclusions drawn.
- Assess the existing evidence on the safety of ECs.

Methods

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines whenever meaningful.

Eligibility criteria

Original articles or abstracts on ECs of any topic relevant to health. Published before 14 Aug 2014 — in any language.

Exclusion criteria

Recommendations, expert statements, reviews, technical reports and other non-original papers. Papers on smoking cessation, abuse liability, nicotine levels, withdrawal symptoms, poisonings, prevalence, attitudes and beliefs.

Search

A search was carried out in PubMed, EMBASE and CINAHL (Appendix 1, detailed search).

Keywords: "electronic cigarette" or "e-cigarette" or "electrically heated cigarette" or "ENDS and cigarette" or "electronic nicotine delivery system" or "electronic nicotine delivery device" or "e-liquid". No limits.

Study selection

We identified 2147 papers (Fig. 1).

Identification

Screening of title left 1101 articles on ECs. After reading the abstract, papers were rejected which did not report a health-related topic. Agreement of authors was necessary to exclude a paper. Papers on symptoms were included even if the main focus of the article was, for example, smoking cessation, leaving n = 271. Out of these, 177 were duplicates, described the same study population or did not report original data, leaving 94 papers. Full documents were obtained for the final inclusion. Additionally, we thoroughly looked through the reference lists of the articles for missed papers and investigated reports for overlooked papers (Anon, 2012, 2013a,b; Burstyn, 2013; Schaller et al., 2013). Eight studies were identified (Anon, 2009; Gennimata et al., 2014; Heavner et al., 2010; Laugesen et al., 2008; Lauterbach and Laugesen, 2012; Lauterbach et al., 2012; Trehy et al., 2011; U.S.Food and Drug Administration, 2009): one was a laboratory analysis (U.S.Food and Drug Administration, 2009)

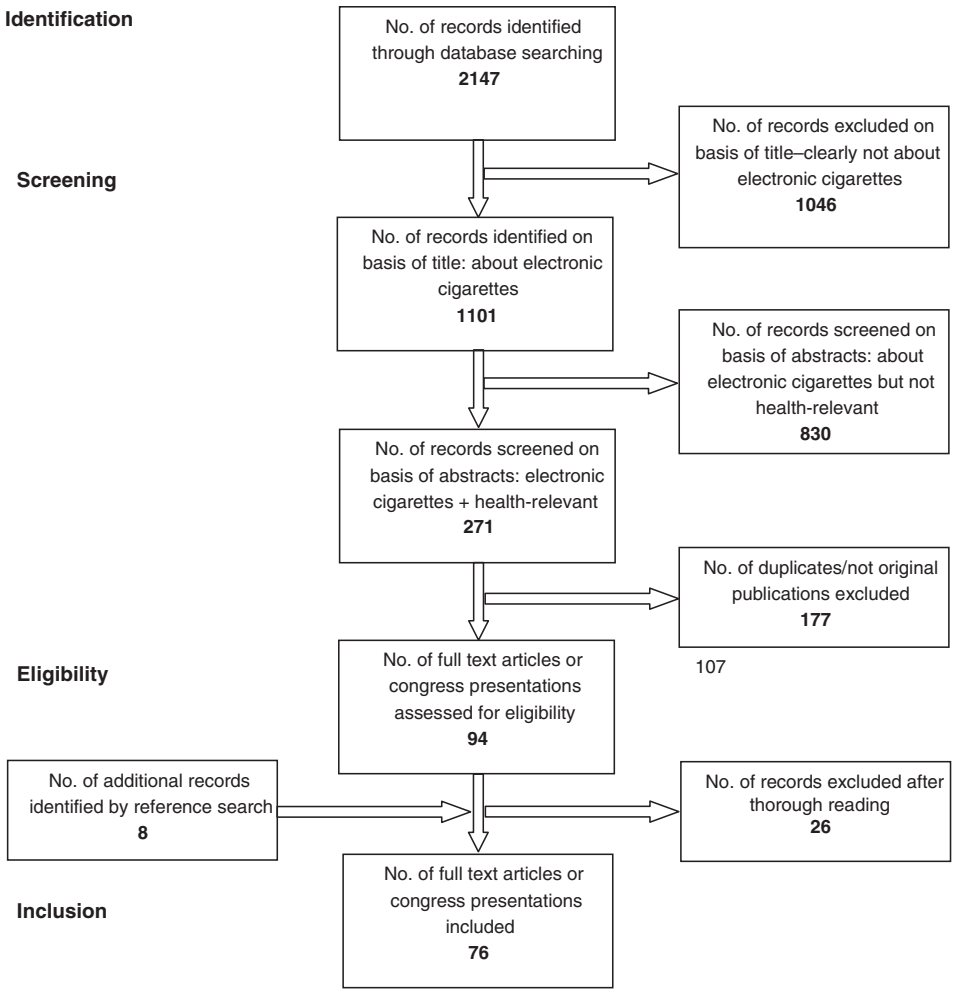

Fig. 1. Flowchart of publications included in the systematic review.

based on data from another identified source (Trehy et al., 2011). Twenty-six were excluded after reading the full text thoroughly (Farsalinos et al., 2013a; Frost-Pineda et al., 2008a,b,c; Horvath, 2012; Kouretas et al., 2012; Martin et al., 2012; Moennikes et al., 2008; Patskan and Reininghaus, 2003; Roemer et al., 2008; Roethig et al., 2005, 2007, 2008; Schorp et al., 2012; Stabbert et al., 2003; Terpstra et al., 2003; Tewes et al., 2003; Tricker et al., 2009, 2012a,b,c,d; Urban et al., 2012; Werley et al., 2008; Zenzen et al., 2012). Two abstracts were later published as a full article (Kouretas et al., 2012), and the remaining articles investigated electrically heated tobacco leaves. None of the additionally included studies have been published as full peer-reviewed articles.

Both authors read and discussed the articles. CP wrote the first draft of the paper. We investigated all papers for conflict of interest, funding and workplace of authors. If in doubt, we contacted the authors and asked about funding and conflict of interest and/or searched the Internet.

Results

Summarizing the evidence

We found 34 studies investigating content/effect of e-fluid or -vapor (Anon, 2009; Bahl et al., 2012; Behar et al., 2014; Bertholon et al., 2013; Cameron et al., 2013; Cervellati et al., 2014; Cheah et al., 2012; Czogala et al., 2014; Etter et al., 2013; Fuoco et al., 2014; Goniewicz et al., 2013a, b, 2014; Hadwiger et al., 2010; Hutzler et al., 2014; Ingebrethsen et al., 2012; Kim and Shin, 2013; Kosmider et al., 2014; Laugesen et al., 2008; Lauterbach and Laugesen, 2012; Lauterbach et al., 2012; McAuley et al., 2012; Park et al., 2014; Pellegrino et al., 2012; Romagna et al., 2013; Ruprecht et al., 2014; Schober et al., 2014; Schripp et al., 2013; Stepanov and Fujioka, 2014; Trehy et al., 2011; Uryupin et al., 2013; Westenberger, 2009; Williams et al., 2013; Zhang et al., 2013), 20 studies reporting adverse events (Bullen et al., 2010; Camus et al., 2014; Caponnetto et al., 2013a,b; Chen, 2013; Dawkins et al., 2013a; Etter, 2010; Farsalinos and Romagna, 2013; Farsalinos et al., 2013b, 2014; Heavner et al., 2010; Hua et al., 2013a; Hureaux et al., 2014; Lee et al., 2013a; McCauley et al., 2012; McQueen et al., 2011; Monroy et al., 2012; Polosa et al., 2011, 2014a; Thota and Latham, 2014), 21 human experimental studies (Battista et al., 2013; Chorti et al., 2012; Czogala et al., 2012; Dawkins and Corcoran, 2013; Dawkins et al., 2012, 2013b; Eissenberg, 2010; Etter and Bullen, 2011a; Farsalinos et al., 2012; Flouris et al., 2012, 2013; Gennimata et al., 2014; Marini et al., 2014; Palamidas et al., 2014; Polosa et al., 2014b; Tsikrika et al., 2014; Vakali et al., 2014; van Staden et al., 2013; Vansickel et al., 2010, 2012; Vardavas et al., 2012) and one animal experimental study (Lim and Kim, 2014). In total, 76 studies (Fig. 1).

Conflict of interest

In 26 studies (34%) the authors had a conflict of interest. Most studies were funded or otherwise supported/influenced by manufacturers of ECs, but several authors had also been consultants for manufacturers of medicinal smoking cessation therapy.

Table 1
Studies investigating the content/effect of fluid or vapor of electronic cigarettes (n = 34).

Name of first author (reference year)	Conflict of interest (yes = ▲)	Reference product	Fluid/ vapor	Conclusion
Bahl et al. (2012)	No	No	○ Fluid	○ Approx. one third of samples were highly cytotoxic to human embryonic stem cells and mouse neural stem cells
Behar et al. (2014)	No	No	○ Fluid	○ Cinnamon flavorings in refill fluids are linked to cytotoxicity
Bertholon et al. (2013)	No	CC and water pipe	○ Vapor	○ Contrary to CC smoke, which has a half-life in air of 19 to 20 min, the half-life of EC is very short and risk of passive "smoking" exposure from EC is modest
Cameron et al. (2013)	No	No	○ Fluid	○ Large variability in nicotine concentrations was found
Cervellati et al. (2014)	No	CC	○ Vapor	○ Exposure to EC vapors is far less toxic than exposure to CC smoke
Cheah et al. (2012)	No	No	○ Fluid	○ Contained nicotine even though they claimed to be nicotine free ○ Significant difference in the nicotine content across EC with same label, brand-to-brand and cartridge-to-cartridge variations ○ Polycyclic aromatic hydrocarbons and TSNAs compounds were not found
Czogala et al. (2014)	▲	CC	○ Vapor	○ Using EC in indoor environments may involuntarily expose non-users to nicotine but not to toxic tobacco-specific combustion products
Etter et al. (2013)	▲Yes	No	○ Fluid	○ Half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia
Fuoco et al. (2014)	No	CC	○ Vapor	○ Particle number distribution modes of the EC-generated vapor were similar to the CC ○ ECs were found to be a major particle source, which can lead to significantly high deposition in vapers
Gennimata et al. (2014)	▲	CC	○ Fluid and vapor	○ There is very little risk of nicotine toxicity from major EC brands in the United Kingdom. ○ Nicotine concentration in e-liquid is not well related to nicotine in vapor ○ None of the tested products reached nicotine concentrations as high as CC
Goniewicz et al. (2013a)	▲Yes	Medicinal nicotine inhalator, CC	○ Vapor	○ Toxic compounds: metals, carbonyls and volatile organic compounds were found in almost all EC, but much lower levels than in CC smoke ○ Vapor of some EC contains traces of carcinogenic nitrosamines ○ Exposure to carcinogenic formaldehyde comparable with CC smoking
Goniewicz et al. (2013b)	▲Yes	No	○ Vapor	○ Vapor contains nicotine, but EC brands and models differ in their efficacy and consistency of nicotine vaporization
Hadwiger et al. (2010)	No	No	○ Fluid	○ Presence of unapproved active pharmaceutical ingredients ○ Nicotine-free products contained nicotine
Hutzler et al. (2014)	No	No	○ Fluid and vapor	○ Many ECs labeled as 'nicotine free' contained nicotine ○ Release of aldehydes is strongly enhanced in the second half of the vaping period ○ The occurrence of aldehydes seems to be associated with lower liquid levels within the cartridges (overheating of the wire?)
Ingebrethsen et al. (2012)	▲Yes	CC	○ Vapor	○ Particle diameters and particle number conc. as in CC smoke
Kim and Shin (2013)	No	No	○ Fluid	○ Almost all fluids contained carcinogenic compounds, tobacco specific nitrosamines ○ High maximum conc. of total tobacco specific nitrosamines ○ Great variability in content of the four measured tobacco specific nitrosamines
Kosmider et al. (2014)	▲	Glycerin, PPG/ mixture of both	○ Vapor	○ ECs might expose their users to the same or even higher levels of carcinogenic formaldehyde than CC smoke ○ Vapors from EC contain toxic and carcinogenic carbonyl compounds ○ Both solvent and battery output voltage significantly affect levels of carbonyl compounds in EC vapors
Anon (2009) (2 versions)	▲Yes	CC	○ Fluid and vapor	○ Very low score for toxic emissions (based on >50 toxicants) ○ Small particle size ○ Mercury detected
Laugesen et al. (2008)	▲Yes	CC	○ Fluid	○ Acetaldehyde, benzene, acrolein and tobacco specific nitrosamines detected at low levels ○ Metals, CO and other VOCs at lower limits than detection
Lauterbach and Laugesen (2012)	▲Yes	CC	○ Vapor	○ Acetaldehyde, formaldehyde, TSNs and mercury detected ○ Compared to CC level of toxins and carcinogens was reduced by >90%
Lauterbach et al. (2012)	▲Yes	CC	○ Vapor	○ Tobacco specific nitrosamines, tar, formaldehyde, acetaldehyde, acrolein, and other toxins found in vapor ○ Most toxicants were reduced by over 98% compared with CC
McAuley et al. (2012)	▲Yes	CC	○ Vapor	○ Ethylbenzene, benzene, toluene, and m/p xylenes acetone, formaldehyde, and acetaldehyde detected ○ Tobacco specific nitrosamines: typically found at lower levels than tobacco smoke ○ Conc. of pollutants were generally orders of magnitude lower than in CC smoke
Park et al. (2014)	No	CC	○ Vapor	○ Preliminary analyses indicate the observed that EC-specific gene expression changes were concordantly changed following CC-conditioned media exposure
Pellegrino et al. (2012)	No	CC	○ Fluid and vapor	○ PG and VG are major ingredients — other ingredients = traces ○ PM in vapor: fine + ultrafine particles ○ PM emissions are significantly lower than in CC smoke
Romagna et al. (2013)	▲Yes	CC	○ Vapor	○ Vapor from 1 out of 21 EC liquids examined had cytotoxic effects on cultured fibroblast ○ CC: significantly higher cytotoxicity
Ruprecht et al. (2014)	No	CC	○ Vapor	○ EC produce less PM than CC and therefore may be less hazardous in terms of secondhand exposure
Schober et al. (2014)	No	No vaping	○ Vapor	○ EC are not emission-free — could be of health concern for users and secondhand smokers ○ Ultrafine particles can be deposited in the lung ○ Release of inflammatory signaling molecule NO
Schripp et al. (2013)	No	CC	○ Vapor	○ Prominent components in the gas-phase: 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, and traces of nicotine ○ Passive vaping must be expected

(continued on next page)

Table 1 *(continued)*

Name of first author (reference year)	Conflict of interest (yes = ▲)	Reference product	Fluid/ vapor	Conclusion
				○ The aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles
Stepanov and Fujioka (2014)	No	No	○ Fluid	○ ECs with the same nicotine content, but different pH, may deliver different doses of nicotine to users ○ Most of the tested brands have basic pH — the long-term effect of chronic aero-digestive tract exposure is not known
Trehy et al. (2011)	No	CC	○ Fluid	○ Some products were found to contain high conc. of nicotine when labeled not to contain nicotine ○ The actual amount of nicotine delivered is likely to be highly variable ○ Transfer of rimonabant and amino-tadalafil to the vapor phase is low ○ Impurity level is lower than for CC
Uryupin et al. (2013)	No	No	○ Fluid	○ The main components of mixtures were non-tobacco products
Westenberger (2009) (FDA)	No	Medicinal nicotine inhalator	○ Fluid	○ Diethylene glycol in one cartridge ○ Detectable levels of carcinogens and toxic chemicals
Williams et al. (2013)	No	CC	○ Fluid and vapor	○ Harmful or potentially harmful elements detected ○ Aerosol: significant amounts of tin and other metals, silicate beads, and nanoparticles, mostly higher than or equal to corresponding conc's in CC smoke ○ Fluid with tin particles was cytotoxic
Zhang et al. (2013)	No	CC	○ Vapor	○ CC produce more particles initially, but particle counts converge to a similar scale as the aerosols condense ○ EC and CC produce aerosols having generally similar particle sizes

CC	conventional cigarette
EC	electronic cigarette
FDA	US Food and Drug Administration
NO	nitric oxide
PM	particular matter
PPG	propylene glycol
TSNAs	tobacco specific nitrosamines
UFP	ultra fine particles
VG	vegetable glycerin
VOCs	volatile organic compounds

Studies reporting content/effect of fluid and/or vapor (Table 1, for details see Appendix 2)

Most studies used CCs as reference and investigated concentrations of several substances known to be toxic/carcinogenic in CCs. Many studies found that the product labels did not show the concentrations of solvents and flavorings.

Glycols

These are the major components in ECs. High amounts of propylene glycol (also called 1,2-propandiol) and glycerin were found in studies testing for these substances (Cheah et al., 2012; Etter et al., 2013; Pellegrino et al., 2012; Schripp et al., 2013; Uryupin et al., 2013).

Nicotine

Several studies found a large variability in nicotine concentrations across brands, labels and cartridges (Cameron et al., 2013; Cheah et al., 2012; Goniewicz et al., 2013b; Hadwiger et al., 2010; Schober et al., 2014; Trehy et al., 2011; Westenberger, 2009), others found smaller variability (Goniewicz et al., 2014). Nicotine-free products were found to contain nicotine, sometimes in high concentrations (Cheah et al., 2012, 2014; Hadwiger et al., 2010; Hutzler et al., 2014; Trehy et al., 2011), while others found that nicotine content corresponded to labels on the bottles (Etter et al., 2013; Laugesen et al., 2008). One study found the concentration of nicotine in vapor to be much lower than in tobacco smoke (Czogala et al., 2014).

Particles

Some studies found that ECs and CCs produce aerosols with comparable particle sizes (Fuoco et al., 2014; Ingebrethsen et al., 2012; Zhang et al., 2013) with fine and ultrafine particles in vapor (Pellegrino et al., 2012), but one study found particles from ECs much smaller (Anon, 2009) and another much bigger (Bertholon et al., 2013) than in tobacco smoke. A study showed that the vapor size distribution alters in the human lung and leads to exhalation of smaller particles (Schripp et al., 2013). Regarding particle concentration, two studies found this to be the same as in tobacco smoke (Fuoco et al., 2014; Ingebrethsen et al., 2012), while three found the concentration to be lower, up to an order of magnitudes lower, than in smoke (Czogala et al., 2014; McAuley et al., 2012; Pellegrino et al., 2012) and one study found that CCs produce more particles initially, but particle counts converge to a level comparable to the condensed vapor Zhang et al., 2013. Two 'real-life' condition studies found that vaping ECs with nicotine showed only marginal particulate matter production in indoor air, while it was much higher after vaping ECs without nicotine (Ruprecht et al., 2014; Schober et al., 2014). The half-life of vapor was found to be very short – seconds – due to rapid evaporation (Bertholon et al., 2013).

Cytotoxicity

One study found that several samples were highly cytotoxic to human embryonic and mouse neural stem cells, and cytotoxicity was due to flavors. Cinnamon had a strong cytotoxic effect (Bahl et al., 2012). E-fluid containing tin particles was found to be cytotoxic on human pulmonary fibroblasts (Williams et al., 2013). However, other studies found that vapor from only one out of 21 e-fluids had cytotoxic effects on cultured murine fibroblasts Romagna et al., 2013 and CCs had significantly higher cytotoxicity (Cervellati et al., 2014; Romagna et al., 2013).

Metals

A study found that concentrations of lead and chromium in vapor were within the range of CCs, while nickel was up to 100 times higher than in CCs Williams et al., 2013. One puff of EC-vapor contained numerous particles, mainly tin, silver, nickel and aluminum. Tin, chromium, and nickel were found as nano-particles. Another study found cadmium, nickel and lead in almost all vapors of 12 brands but the amounts of toxic metals were low, comparable with amounts contained in a nicotine inhaler (nicotine replacement treatment, NRT) (Goniewicz et al.,

2013a). Finally, some studies found metals in fluid at lower limits than detection (Laugesen et al., 2008) and trace quantity of mercury in vapor (Anon, 2009). A 'real-life' study showed a 2-fold increase of aluminum in indoor air after vaping (Schober et al., 2014).

Tobacco-specific nitrosamines (TSNAs)

Some studies found high maximum concentrations of total TSNAs in the vapor of most (Goniewicz et al., 2013a), or almost all fluids (Kim and Shin, 2013). Other studies found carcinogenic TSNAs present in vapor at lower levels than tobacco smoke (McAuley et al., 2012) or at trace levels (Lauterbach and Laugesen, 2012; Lauterbach et al., 2012). Some studies detected TSNAs with no/weak carcinogenic effect or no TSNAs in the fluid (Cheah et al., 2012; Etter et al., 2013; Schober et al., 2014; Westenberger, 2009).

Carbonyls

In one study the potential human carcinogens formaldehyde, acetaldehyde and acrolein were detected in the vapors of almost all ECs (Goniewicz et al., 2013a). Exposure to formaldehyde was comparable with smoking (Goniewicz et al., 2013a), as was also the case with vapor from high-voltage devices (Kosmider et al., 2014). The highest levels of carbonyls were observed in vapors generated from propylene glycol-based solutions (Kosmider et al., 2014) or in the second half of a vaping period, indicating overheating of wires (Hutzler et al., 2014). A study concluded that most carbonyls were detected at low concentrations in vapor, with the exception of acetone, formaldehyde, and acetaldehyde (McAuley et al., 2012). Formaldehyde, acetaldehyde and acrolein were also found in another study, at concentrations approx. 1/10 of those in smoke from CCs (Lauterbach et al., 2012). One study found acetaldehyde and formaldehyde at low levels (Lauterbach and Laugesen, 2012) and another found acetaldehyde and acrolein in vapor at low levels (Laugesen et al., 2008). The same author presented similar findings in another study, but in a newer version of the same abstract, acetaldehyde and acrolein were not mentioned (Anon, 2009). Finally, one study found that the release of formaldehyde was below the limit of detection (Schripp et al., 2013).

Volatile organic compounds (VOCs) such as toluene Czogala et al. (2014) and p,m-xylene were identified in almost all vapors (Goniewicz et al., 2013a). In one study, the concentrations were below the level of detection (McAuley et al., 2012).

Polycyclic aromatic hydrocarbons (PAHs)

Studies found either no PAHs in fluid (Cheah et al., 2012), or that most PAHs were below detection level (Lauterbach and Laugesen, 2012; McAuley et al., 2012) or as traces, only (Lauterbach et al., 2012). However, probably carcinogenic PAHs in indoor air increased by 20% after vaping (Schober et al., 2014).

Other measures

Human bronchial cells that contained mutations found in smokers at risk of lung cancer were grown in a culture medium that had been exposed to vapor. The researchers found that cells exposed to high-nicotine vapor showed a similar pattern of gene expression to those exposed to tobacco smoke (Park et al., 2014). A study found that vapor induced the release of cytokines and pro-inflammatory mediators (Cervellati et al., 2014). Another study found that half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia (Etter et al., 2013). The highly toxic diethylene glycol was found in one cartridge in one study (Westenberger, 2009) but not in another (Etter et al., 2013). One study found potentially harmful additives, such as coumarin (Hutzler et al., 2014). Products advertised as containing tadalafil contained amino-tadalafil (Hadwiger et al., 2010; Trehy et al., 2011). Products advertised as containing rimonabant, contained rimonabant plus an oxidative impurity of rimonabant (Hadwiger et al., 2010). One study found significant amounts of silicate beads in the aerosol (Williams et al., 2013). Most nicotine-containing ECs have a basic pH > 9, which seems to influence the doses of nicotine delivered (Stepanov and Fujioka, 2014).

Studies reporting adverse events (Appendix 3)

Reports on AE were often flawed by selection bias. In most cases of the reporting of adverse events causality could not be confirmed. Therefore, and due to limited space, we present details on AE in Appendix 3 only. No serious AE were reported in controlled prospective studies. Most AE have been from the mouth/throat and the respiratory system, but symptoms from many organ systems have been reported. On the other hand, many regular EC users reported decrease in respiratory symptoms and improvements in general health.

Human experimental studies (Table 2, for details see Appendix 4)

Most studies included smokers as volunteers and compared with a reference, mostly own-brand CCs.

Adverse events (AE)

These were very similar to those reported in Appendix 3. There was low reporting of AE in regular users, who were EC-naïve before study start, with the most frequent being light-headedness, throat irritation, dizziness, cough (Dawkins and Corcoran, 2013; Vakali et al., 2014; van Staden et al., 2013).

Pulmonary system

Studies in EC-naïve smokers found that the same particle dose was received as with smoking and vaping (Marini et al., 2014), increased airway resistance (Marini et al., 2014; Palamidas et al., 2014; Vardavas et al., 2012) and a concomitant decrease in specific airway conductance (Palamidas et al., 2014), an increase in impedance and overall peripheral airway resistance (Vardavas et al., 2012); effects that are reminiscent of those seen with tobacco smoking. Two studies found immediate reductions in exhaled nitric oxide, similar to smoking (Marini et al., 2014; Vardavas et al., 2012) and increased the release of the inflammatory signaling molecule NO upon inhalation (FeNO) (Schober et al., 2014) while another study found a decrease in FeNO (Vakali et al., 2014). A study including both healthy volunteers and patients with asthma and chronic obstructive pulmonary disease also showed that 10 min of vaping caused immediate significant airway obstruction (Gennimata et al., 2014) which is in contrast with a retrospective review finding objective and subjective improvements in asthma outcomes (Polosa et al., 2014b.) Another study found that short-term usage was associated with increased flow resistance even though spirometry-assessed lung function was deemed normal (Chorti et al., 2012). Passive, but not active vaping of one EC resulted in short-term lung obstruction, indicating insufficient inhalation by EC-naïve smokers (Chorti et al., 2012). The last study found that short-term vaping of ECs generated non-significant decrease in lung function; approx. half of what was seen in smoking (Flouris et al., 2013).

Cardiovascular system

Some studies in EC-naïve smokers found that short-term vaping resulted in increased heart rate (Battista et al., 2013; Czogala et al., 2012; Tsikrika et al., 2014; Vakali et al., 2014; Vansickel et al., 2012), an elevation in diastolic blood pressure (Battista et al., 2013; Czogala et al., 2012), and a decrease in oxygen saturation (Vakali et al., 2014). Other studies found no increase in heart rate (Eissenberg, 2010; van Staden et al., 2013; Vansickel et al., 2010) or in blood pressure (van Staden et al., 2013) but an increase in oxygen saturation (van Staden et al., 2013). Active and passive vaping in EC-naïve smokers did not influence the complete blood count (Flouris et al., 2012). One study using experienced EC-users found a slight elevation in diastolic blood pressure, but no effect on cardiac function (Farsalinos et al., 2012).

Table 2
Human experimental studies reporting health effects (n = 21).

Name of first author (reference year)	Conflict of interest ▲ = Yes	Reference product	Method Length of exposure	Numbers of participants	Conclusions
Battista et al. (2013)	No	CC	○ Experimental study ○ Exposure: 4 min of smoking/ vaping	○ 12 regular users of EC	○ EC inhalation produces the same patho-physiological cardiovascular effects of CC smoking
Chorti et al. (2012)	No	CC	○ Volunteers in CC group smoked 2 CC ○ Volunteers in EC group puffed 1 EC	○ 15 EC naive heavy-smokers	○ Passive but not active EC vaping resulted in short-term lung obstruction and increased cotinine
Czogala et al. (2012)	No	CC	○ A repeated measures design ○ Exposure: 5 min of smoking/ vaping	○ 42 EC naive daily smokers	○ Slight non-sign elevation in diastolic blood pressure, pulse and carboxyhemoglobin
Dawkins and Corcoran (2013)	▲	No	○ A repeated measures design ○ Exposure: 1) Ten puffs 2) 1 h ad lib use	○ 14 regular EC users	○ Low reporting of AE in regular users. Most frequent: light-headedness, throat irritation and dizziness
Dawkins et al. (2013b)	▲	0 mg nicotine EC	○ Within-subjects design ○ Exposure: 10 min ad lib use	○ 20 EC naive smokers	○ EC can effectively deliver nicotine to impact on cognitive performance; improved time-based memory
Dawkins et al. (2012)	▲	0 mg nicotine EC	○ Mixed experimental design ○ Exposure: 5 min ad lib use	○ 86 EC naive smokers	○ Improved nicotine withdrawal impaired concentration/ memory
Eissenberg (2010)	No	CC	○ Hemodynamic measurements ○ Exposure: Puffed ad libitum 10 times	○ 16 EC naive smokers	○ No increase in heart rate
Etter and Bullen (2011a)	No	No	○ Saliva sampling in current vapers ○ Exposure: daily vaping	○ 31 current users (30 daily users) of EC	○ Cotinine levels in experienced vapers were similar to levels previously observed in smokers and higher than in users of nicotine replacement therapy
Farsalinos et al. (2012)	No?	CC	○ Hemodynamic measurements + echocardiogram at baseline and after smoking/vaping ○ Exposure: 1 CC or 7 min of vaping of EC	○ 20 EC naive smokers and 20 EC users	○ Slight elevation in diastolic blood pressure but no effect on cardiac function in experienced EC users
Flouris et al. (2013)	No	CC	○ Repeated-measures controlled study ○ Exposure: 30 min of active/passive smoking or vaping	○ 15 EC naive smokers and 15 never-smokers	○ Short term passive vaping generated small non-sign decrease in lung function, approx. the half of smoking ○ Similar nicotinergic impact to CC
Flouris et al. (2012)	No	CC	○ Three experimental sessions; active and passive exposure ○ Exposure: 2 CC within 30 min or 'a number of puffs' within 30 min	○ 15 EC naive smokers and 15 never-smokers	○ Acute active and passive vaping did not influence complete blood count indices in smokers and never smokers
Gennimata et al. (2014)	No?	?	○ Exposure: vaping for 10 min	○ 8 never smokers and 24 EC naive smokers	○ Short-term exposure caused immediate airway obstruction
Marini et al. (2014)	No	CC	○ Experimental study ○ Exposure: 4 puffs	○ 25 smokers	○ Similar effect on human airways, and same particle dose received with smoking and vaping
Palamidas et al. (2014)	No	No	○ Experimental study ○ Exposure: Gr. A: vaping in 10 min	○ 70 volunteers (27 with asthma/COPD). Smokers + never smokers	○ Increased airway resistance and a concomitant decrease in specific airway conductance
Polosa et al. (2014b)	▲	No	○ Retrospective review of changes in lung function and asthma control ○ Exposure: 6 and 12 months follow-up	○ 18 smoking asthmatics who switched to regular EC use	○ Study indicates that regular use of EC to substitute smoking is associated with objective and subjective improvements in asthma outcomes
Tsikrika et al. (2014)	No	No	○ Experimental study ○ Exposure: vaping in 10 min	○ 62 volunteers, non-smokers + smokers: 28 with COPD/asthma	○ Increased heart rate and symptoms like cough and sore throat
Vakali et al. (2014)	No	No	○ Experimental study ○ Exposure: vaping in 10 min	○ 64 volunteers, non-smokers + smokers	○ Increased heart rate, palpitations and a decrease in SpO_2 ○ A decrease in fraction of exhaled nitric oxide
van Staden et al. (2013)	▲	No	○ A single group within-subject design ○ Exposure: switch to EC vaping in 2 weeks	○ 15 smokers switched to EC, 2 drop-outs	○ Increase in oxygen saturation, no changes in blood pressure and pulse rate, cough worse/improved ○ Phlegm increased in some but decreased in more
Vansickel et al. (2010)	No	CC	○ Repeated-measures controlled study ○ Exposure: two, 10-puff EC bouts	○ 32 EC naive heavy smokers	○ No changes in plasma nicotine and heart rate ○ No increase in CO
Vansickel et al. (2012)	No	CC	○ 4 within-subject sessions ○ Exposure: six 10-puff bouts-separated by 30-mins	○ 20 EC naive heavy smokers	○ Increase in heart rate
Vardavas et al. (2012)	No	EC with cartridge removed	○ Exposure: ad lib use for 5 min	○ 30 EC naive smokers of at least 5 pack years	○ Increased flow resistance ○ Immediate adverse effects on the airways after short-term use; similar to some of the effects seen with smoking

EC = electronic cigarette; CC = conventional cigarette.

Cognitive function

Two studies found improved time-based but not event-based prospective memory (Dawkins et al., 2013b) and improved nicotine withdrawal impaired concentration/memory (Dawkins et al., 2012).

Other

A metabolite of the pyrolysis product acrolein was found in urine, after vaping ECs with nicotine (Schober et al., 2014).

Animal study (Table 3, for detail see Appendix 5)

One study in mice treated intratracheally with EC fluid increased the infiltration of inflammatory cells, aggravated asthmatic airway inflammation and airway hyper-responsiveness, and stimulated the production of cytokines and ovalbumin-specific IgE production (Lim and Kim, 2014).

Discussion

Interpreting the findings

Our review included 76 studies investigating the health effects of ECs. We included studies investigating content of ECs, reports on adverse events, animal experiments and human experimental studies. Due to the many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results and the lack of long-term follow-up, no firm conclusions can be drawn on the safety of ECs, and much is left to subjective interpretations.

A substantial number of studies were funded or otherwise supported by manufacturers of ECs. Conflict of interest seems to influence the conclusions of these papers. The content of e-liquid and vapor is characterized by high amounts of propylene glycol, and sometimes glycerin, nicotine and flavors. Many ECs contain misleading/missing information on product ingredients, especially nicotine, and many studies found harmful substances: fine/ultrafine particles, cytotoxicity, harmful metals, carcinogenic tobacco-specific nitrosamines and carbonyls — some in most samples, others in few. Some studies found a high concentration of harmful substances, as high as in CCs or higher, but more studies found low or trace levels. Some flavors, such as cinnamon were found to have strong cytotoxic effects. One experimental in vitro study found that EC vapor can change gene expression in a similar way to tobacco. Higher battery-output voltage increased the production of harmful substances substantially, which was also the case with propylene glycol-based solutions and when e-liquid levels decreased. The dangers of secondhand exposure have not been thoroughly evaluated. A potentially carcinogenic pyrolysis product was found in urine. Lungs are the primary target organ and experimental studies have found effects after very short-term exposure that are reminiscent of the obstructive effects seen with smoking, even though the impact on lung function was smaller than with smoking. An animal study found that EC fluid can exacerbate allergy-induced asthma symptoms. A few experimental studies have shown that ECs can effectively deliver nicotine to impact on cognitive performance and the heart. Case reports on different lung diseases and atrial fibrillation found time association and/or reversibility, but causality can only be hypothesized. No serious AE were reported in controlled prospective studies. No serious AE were reported in controlled prospective studies. Most AE have been from the mouth/throat and the respiratory system, but symptoms from many organ systems have been reported. Regular EC users often reported improvements in respiratory symptoms and general health. Findings were flawed by selection-bias.

This research field is new and very challenging. Serious methodological problems were identified. Core problems are: 1) Any research only applies to the specific EC brand, model and batch tested, with no certainty that the findings will apply to other or future brands, models or batches. ECs are subject to frequent modifications, and there are currently more than 460 brands. 2) Almost all studies have compared concentrations of harmful substances in CCs with concentrations in ECs, but health hazards may be different than from smoking. 3) EC-use topography is significantly different than smoking (Hua et al., 2013a). When vaping, you are sucking harder and have longer puffing duration, approx. double of smoking, especially if the fluid content in the cartridge is low (Hua et al., 2013b). Therefore, the real uptake of harmful substances might be underestimated when testing on EC-naïve volunteers or standard smoking machines. Also, studies show significant variations in puffing topography among users of various EC models (Farsalinos et al., 2013a), that production of harmful substances is influenced by both battery voltage output (Kosmider et al., 2014) and e-liquid levels left (Hutzler et al., 2014), and that pH may influence the doses of nicotine delivered to users (Stepanov and Fujioka, 2014) — this complicates the research even more. 4) Human experiments were mostly based on very short-term exposure, e.g. vaping for a few minutes — not reflecting real-life exposure.

Of special concern are compounds *not* found in CCs: the glycols, propylene glycol and glycerin, major ingredients of ECs. Propylene glycol, which creates the visible fume, is a solvent used in pharmaceutical products and is "generally recognized as safe" (Anon, 2011). An internal technical report commissioned by vapers and vendors of ECs concluded that estimated levels of exposure to propylene glycol and glycerin are close enough to threshold-limit values to warrant concern and that the threshold-limit values are based on uncertainty rather than knowledge (Burstyn, 2013). Volunteers exposed to propylene glycol mist for 1 min developed a slight airway obstruction and increased self-rated severity of dyspnea (Wieslander et al., 2001). Long-term exposure to propylene glycol has been found to exacerbate and/or induce multiple allergic symptoms in children (Choi et al., 2010). Experimental studies show moderate cytotoxic effect on skin fibroblasts (Ponec et al., 1990), irritation to the upper respiratory tract and squamous metaplasia of the epiglottis following exposure at concentrations present in ECs (Renne et al., 1992). Ethylene glycol, associated with pronounced toxicological risks (Hess et al., 2004), has been found to replace glycerol/

Table 3
Animal experimental studies reporting health effects (n = 1).

Name of first author (reference year)	Conflict of interest ▲=Yes	Reference product	Animal type and number	Exposure	Conclusions
Lim and Kim (2014)	No	CC	○ 24 five-week-old female BALB/c mice	○ Diluted solution was intra-tracheally instilled to ovalbumin -sensitized mice two times a week for 10 weeks	○ Suggest that the inhalation of EC solutions can function as an important factor to exacerbate the allergy-induced asthma symptoms

EC = electronic cigarette; CC = conventional cigarette.

propylene glycol in several brands (Hutzler et al., 2014). Other concerns are flavors, metals, rubber, silicone and ceramics. Significant amounts of metals (probably originating from solder joints, wires etc.) and silicate beads (probably from fiberglass wicks) have been found in ECs (Williams et al., 2013). Occupational exposure to silicate dusts can cause extensive pulmonary damage (Elmore, 2003). Lead and chromium concentrations were found within the range of CCs, nickel was up to 100 times higher than in CCs and e-fluid containing tin was found to be cytotoxic (Williams et al., 2013). These metals appear on the U.S. Food and Drug Administration's "Harmful and Potentially Harmful Chemicals" list (FDA, 2014).

Many of the harmful substances detected were identified at very low concentrations but we are dealing with intense and chronic exposure. Values below the threshold limit don't necessarily protect against the health effect of 200–300 daily inhalations (Goniewicz et al., 2013b) over decades — harm might accumulate over years/decades, as with CCs. Further, the presence of, for example, ten substances below the official threshold-limit values may add up in a synergic way and the safety of the combination of substances has not been evaluated. The inhaled aerosol may undergo changes in the human lung (Schripp et al., 2013). Long-term inhalation of an aerosol may increase the risk of tuberculosis, as observed in tobacco smoking (Bates et al., 2007). Additionally, there is enough heat generated during puffing (Schripp et al., 2013) to cause the fluid to decompose and/or components of the device to pyrolyze, whereby toxic/carcinogenic substances may be formed. Flavors are also known to affect the stability of products.

Discussions about levels of potentially harmful compounds in ECs often remove the focus from the fact that we are dealing with a very efficient nicotine delivery system. Almost all regular users report that they use ECs with nicotine (Etter and Bullen, 2011b), with levels in EC users (Etter and Bullen, 2011a) as in smokers (Etter et al., 2000), and higher than in NRT users (Benowitz et al., 1997). It is well established that nicotine is highly addictive (Benowitz, 1999; Picciotto and Corrigall, 2002). More than 60% of smokers wish to quit because they don't like being dependent (Pisinger et al., 2011) and switching to ECs does not break the nicotine addiction.

Nicotine is referred to by some health professionals as harmless, whereas others do not share this view (National Center for Chronic Disease Prevention and Health Promotion, 2014). A meta-analysis found no increased risk of serious adverse events (Moore et al., 2009). To our knowledge, only one study has investigated the health effects of long-term pure nicotine/NRT use, finding no increase in the risk of cancer (Murray et al., 2009). However, nicotine has a significant biologic activity: in the central nervous system nicotine stimulates the release of important neurotransmitters and hormones (Balfour, 1982), and in the peripheral system it stimulates the release of catecholamines, with effects such as vasoconstriction, increase in heart rate and myocardial contractility (Kilaru et al., 2001). Animal studies suggest that nicotine accelerates atherosclerosis (Kilaru et al., 2001), reduces sperm quality (Condorelli et al., 2013), promotes growth of cancer cells and the proliferation of endothelial cells, reduces the responsiveness of several cancers to chemotherapy (Al-Wadei et al., 2009; Banerjee et al., 2013; Catassi et al., 2008; Dinicola et al., 2013; Petros et al., 2012), and fetal and neonatal nicotine exposure leads to widespread adverse postnatal physical and mental health consequences (Bruin et al., 2010; Dwyer et al., 2009; Gao et al., 2008). The applicability to human beings may be questioned. Poison centers are receiving many calls regarding e-fluid (Kilaru et al., 2001); mostly exposures have resulted in minimal toxicity (Vakkalanka et al., 2014), but a case of fatal nicotine poisoning in a child has been reported (Kloosterman, 2013).

Health professionals who advocate "harm reduction" compare ECs with CCs, focus on smokers only, believe that ECs have no negative long-term health effects, that nicotine is a harmless recreational drug and that smokers are unwilling/unable to quit. These views are strongly supported by the EC/tobacco industry. On the other hand, health professionals working with public health point out that CCs are the most harmful legal products on the market (everything seems safe compared to smoking) and fear potential long-term health hazards. Other major concerns are that the product is spreading to never-smokers and ex-smokers, citizens unexposed to CCs, that many smokers have dual use (using both products) or switch instead of quitting, and that widespread EC-use will re-normalize smoking. This view is supported by the medical industry producing smoking cessation products.

Are there good reasons for concern? It would be naïve not to expect that the manufacturers will try hard to spread the use of their product to as many consumers as possible; it is a billion dollar business and history has shown that the tobacco industry has no ethical constraints and has used every iteration of cigarette design to undermine prevention and cessation (Bero, 2005; Proctor, 2011).

For several years ECs have been used as a healthier alternative to smoking or as an aid to cut down or quit (Adkison et al., 2013; Etter and Bullen, 2011b; Goniewicz et al., 2013c). Some prospective studies were very promising about ECs' effect as a smoking reduction/cessation aid (Caponnetto et al., 2013a,b), and a recent 'real-life' study showed that ECs increased cessation rates more than no aid/NRT bought over the counter (Kotz et al., 2014). However, a meta-analysis based on population studies found that EC users were significantly less likely than non-users to have stopped smoking (Grana et al., 2014), a longitudinal study in cancer patients showed that EC-users were twice as likely to be smoking at the time of follow-up as non-users (Borderud et al., 2014), and the only existing randomized smoking cessation study showed that ECs were not significantly more effective than nicotine patch therapy (Bullen et al., 2013). A survey sponsored by EC manufacturers found that only 1% of EC users achieved permanent abstinence by the use of ECs (Heavner et al., 2010); this study is not cited by harm reduction advocates. There is evidence that ECs are often used for dual use (Adkison et al., 2013; Etter, 2010; Etter and Bullen, 2011b; Lee et al., 2013b), as a supplement to CCs e.g. in places with a smoking ban, by ex-smokers (Adkison et al., 2013; Anon, 2013c; Etter, 2010; Etter and Bullen, 2011b) and by smokers who planned to quit but instead switched to long-term use of ECs, thereby undermining complete cessation (Bullen et al., 2013). An experimental study showed that EC exposure may evoke smoking urges in young adult daily smokers (King et al., 2014). The last few years EC-use has spread to minors and experimental use has doubled within one year (Anon, 2013c; Anon, 2013d; Camenga et al., 2014). Surveys show that a high proportion of adolescents have tried ECs (Goniewicz and Zielinska-Danch, 2012; Dautzenberg et al., 2013; Czoli et al., 2014), even children as young as 12–14 years (Dautzenberg et al., 2013). Of special concern is that young never-smokers are experimenting with ECs (Anon, 2013c,d; Czoli et al., 2014; Dautzenberg et al., 2013; Goniewicz and Zielinska-Danch, 2012). A survey found that every fifth of those who were non-smokers when they started using ECs were also smoking at time of survey, but there was no information as to whether they were never-smokers or ex-smokers at initiation of EC-use (Goniewicz et al., 2013c). To our knowledge, no studies have investigated whether ECs are a gateway to smoking.

It is necessary to include all users and modes of use when discussing benefits or risks of ECs. Additionally, the use of ECs might undermine decades of efforts to denormalize smoking (Choi et al., 2012).

We find that it is of concern that the safety, manufacture, quality control, labeling, sales and marketing of a product with unknown long-term health consequences and exploding sales is more or less unregulated. Authorities have a responsibility to ensure that EC-users can buy safe high-quality products with contents corresponding to the label, and they also have the responsibility to prevent the spread of the use of ECs to minors and non-smokers. Also, they must keep in mind that the impact of a product on public health is determined by two factors: 1) the degree of toxicity/harm of the substance; and 2) how widespread the exposure is. Even if ECs are less harmful than CCs, the product may have a very negative impact on public health if the use is spread to a large part of the population; ECs might achieve popularity as high as that of CCs in the 1950s or 60s, before evidence

and an awareness of harm became widespread in the population. Health professionals and decision-makers must exercise the utmost caution in trusting conclusions of studies/reviews where there is a conflict of interest (Bero, 2005; Brezis, 2008; Proctor, 2011). Systematic research is urgently needed (Etter et al., 2011).

Conclusion

Due to the many methodological problems, the relatively few and often small studies, the inconsistencies and contradictions in results and the lack of long-term results, no firm conclusions can be drawn on the safety of ECs. A substantial number of studies were published by authors with a conflict of interest and we must exercise the utmost caution in trusting their conclusions. Based on 76 studies, ECs cannot be regarded as safe, even though they probably are less harmful than CCs. The "harm reduction" strategy might be a gain for smokers reluctant to quit but ex- and never-smokers probably have an increased risk by using ECs. Combined with the imminent risk of undermining smoking cessation and the renormalization of smoking the total risk on public health from widespread use of ECs might be substantial. Their use should, so far, be restricted to smokers unwilling/unable to quit. Systematic research is urgently needed.

Conflict of interest
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Contributors

CP and MD were responsible for the conception and design. Both authors analyzed and interpreted the data and revised the article for important intellectual content. CP drafted the article and is guarantor.

Competing interests

Both authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Not required.

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E-Cigarettes and Potential Implications for Plastic Surgery

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Summary: The use of tobacco-based products, most notably cigarettes, is related directly to wound healing problems and poorer outcomes in plastic surgery. Current abstracts have highlighted the potential complications from nicotine, specifically following plastic surgery in patients who choose to smoke. Recently, products that use electricity to vaporize liquid nitrogen have been gaining popularity. New rules were recently proposed that would give the federal government authority over electronic cigarettes. However, the health-related issues surrounding e-cigarettes are still largely unknown or misunderstood. These issues also extend to their impact on surgical procedures, notably their effect on plastic surgical procedures that rely heavily on the vascularity of either the host wound bed or the replacement tissue. (*Plast. Reconstr. Surg.* 138: 1059e, 2016.)

Broad consumer use of cigarettes began in the 1920s, coinciding with the marketing and advertising of the product that glamorized and subsequently popularized their use. It took nearly a generation for the deleterious health effects to be manifested, so that by the 1940s, lung cancer rates had exploded. To date, tobacco-related products have killed more Americans than all the wars in which Americans have fought. By the next generation, in the 1960s, the federal government took an interest in alerting the public to the severe health risks associated with smoking and attempting to make tobacco products safer. The Surgeon General of the United States in 1964 issued a report that definitively linked smoking to lung cancer. He went further to describe research into new kinds of cigarettes as "a promising avenue for further development." Over the ensuing decade, legislation outlawed certain forms of cigarette advertising, and warning labels were prominently displayed on cigarette packages or in advertisements. The iconic Times Square advertisement with smoke rings being exhaled from a billboard image disappeared. The concept of developing "safer" tobacco products with lower tar and nicotine continued in the 1970s and 1980s, with the government spending close to $6 million per year to try to develop safer tobacco products. As late as 1981, low-tar and low-nicotine brands were touted as healthier alternatives for smokers who could not or would not quit traditional products.[1] As a result, domestic smoking rates since the 1960s have declined sharply but have leveled off at approximately 18 percent. In the early 1990s, David Kessler, the head of the U.S. Food and Drug Administration, in a landmark declaration, recognized cigarettes as a nicotine delivery system. The turn of the century was marked by huge class-action litigation against cigarette manufacturers by primary and secondary smokers. Today, cigarette smoking remains the single largest cause of preventable death in the United States, directly or indirectly responsible for contributing to the mortality of 480,000 people per year.

The idea of an electronic cigarette (or "e-cigarette" or "e-cig") is traced to 1963, when Herbert Gilbert filed a patent for this type of product. The idea, however, was seemingly ahead of its time. The technology was lacking

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Wound Healing and Infection in Surgery

The Clinical Impact of Smoking and Smoking Cessation: A Systematic Review and Meta-analysis

Lars Tue Sørensen, MD

Objectives: To clarify the evidence on smoking and postoperative healing complications across surgical specialties and to determine the impact of perioperative smoking cessation intervention.

Data Sources: Cohort studies and randomized controlled trials.

Study Selection: Selected studies were identified through electronic databases (CENTRAL, MEDLINE, and EMBASE) and by hand searching.

Data Extraction: Multiple data on study characteristics were extracted. Risk of bias was assessed by means of the Newcastle-Ottawa Scale and Jadad score. Healing outcome was classified as necrosis, healing delay and dehiscence, surgical site infection, wound complications, hernia, and lack of fistula or bone healing. Mantel-Haenszel and inverse variance methods for meta-analysis (fixed- and random-effects models) were used.

Data Synthesis: Smokers and nonsmokers were compared in 140 cohort studies including 479 150 patients. The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing. Former smokers and patients who never smoked were compared in 24 studies including 47 764 patients, and former smokers and current smokers were compared in 20 studies including 40 629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications combined. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).

Conclusions: Postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. Perioperative smoking cessation intervention reduces surgical site infections, but not other healing complications.

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FOR THE PAST DECADES, A growing amount of literature has shown that smoking has a negative effect on postoperative outcome. A recent study disclosed that postoperative mortality and morbidity in smokers are substantial.[1]

See Invited Critique at end of article

Until now, no general survey on the clinical impact of smoking on postoperative healing has been published, and the literature is dispersed across operations and surgical specialties. The evidence on the impact of smoking cessation on healing complications is sparse, and only a few studies have assessed how long patients must be abstinent from smoking before surgery to reduce the risk. Accordingly, it is not clear if the effort, which is necessary to ensure successful abstinence from smoking, is worthwhile in terms of reducing healing complication rates. Recently published systematic reviews have disclosed that preoperative smoking cessation intervention reduces postoperative complications overall.[2,3] However, these reviews assessed pooled postoperative outcome and did not address healing complications.

The aims of this systematic review were to describe the association between smoking and healing complications across all surgical specialties and to estimate the impact of perioperative smoking cessation on postoperative healing outcomes.

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Table 1. Search Strategy[a]

Strategy	Cohort Studies	Intervention Studies
Short-term outcome (≤30 postoperative days)	Postoperative morbidity OR postoperative complication* OR wound complication* OR wound healing complication* OR surgical wound infection OR surgical site infection OR wound infection OR mesh infection OR delayed healing OR wound dehiscence OR wound rupture OR wound disruption OR wound separation OR wound necrosis OR tissue necrosis OR skin necrosis OR epidermolysis OR flap necrosis OR flap failure OR flap loss OR mesh erosion OR anastomotic leak* OR fistula	Postoperative morbidity OR postoperative complication* OR wound complication* OR wound healing complication* OR surgical wound infection OR surgical site infection OR wound infection OR mesh infection OR delayed healing OR wound dehiscence OR wound rupture OR wound disruption OR wound separation OR wound necrosis OR tissue necrosis OR skin necrosis OR epidermolysis OR flap necrosis OR flap failure OR flap loss OR mesh erosion OR anastomotic leak* OR fistula
Long-term outcome (>30 postoperative days)	Delayed healing OR hernia OR incisional hernia OR hernia recurrence OR pseudarthrosis OR nonunion OR fistula	Delayed healing OR hernia OR incisional hernia OR hernia recurrence OR pseudarthrosis OR nonunion OR fistula
Clinical context	Smoking OR tobacco use OR nicotine	Smoking cessation OR tobacco use cessation OR smoking reduction OR tobacco use reduction OR nicotine drugs OR nicotine replacement therapy
Search filter	None	EMBASE: (1) RCT; (2) randomization; (3) controlled study; (4) multicenter study; (5) phase III clinical trial; (6) phase IV clinical trial; (7) double-blind procedure; (8) single-blind procedure, (9) ([singl* OR doubl* OR trebl* OR tripl*]) adj [blind* OR mask*]).ti,ab; (10) (random* OR cross* over* OR factorial* OR placebo* OR volunteer*).ti,ab; (11) 6 OR 3 OR 7 OR 9 OR 2 OR 8 OR 4 OR 1 OR 10 OR 5; (12) "human*".ti,ab; (13) (animal* OR nonhuman*).ti,ab; (14) 13 AND 12; (15) 13 not 14; (16) 11 not 15 MEDLINE: (1) RCT.pt; (2) controlled clinical trial.pt; (3) randomized.ab; (4) placebo.ab; (5) clinical trial.sh; (6) randomly.ab; (7) trial.ti; (8) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; (9) humans.sh; (10) 8 AND 9
Databases searched	CENTRAL, MEDLINE, and EMBASE. Search terms were applied as MeSH and free text. To validate the search strategy a sampled cross-search strategy with the search terms "risk factor*" AND "postoperative complication*" was applied.	CENTRAL, MEDLINE, and EMBASE. Search terms were applied as MeSH and free text.

Abbreviations: ab, abstract; MeSH, medical subject headings; pt, publication type; RCT, randomized controlled trial; sh, subject heading; ti, title.
[a]Search strategies included the short- or long-term outcomes and clinical context and search filter. An asterisk indicates a truncated search term.

METHODS

SEARCH STRATEGY

Computerized searches in the CENTRAL, MEDLINE, and EMBASE databases were performed under supervision from a Cochrane Collaboration information specialist to identify relevant studies (**Table 1**). In addition, a manual cross-reference search of all potentially eligible articles retrieved for full-text evaluation was undertaken. The searches and study retrieval were performed until May 2010 for cohort studies and January 2011 for randomized controlled trials (RCTs).

STUDY ELIGIBILITY

Cohort studies with 100 patients or more assessing healing complications in smokers and former smokers were included to ensure that a broad range of surgical procedures and healing complications were addressed. Studies assessing multiple operations or healing outcomes from the same patient cohort were included according to each specified operation or healing outcome.

Randomized controlled trials assessing the effect of perioperative smoking cessation on postoperative healing complications were included. This intervention embraced all types of behavioral or motivational counseling with or without pharmacotherapy. Only RCTs with a minimum of 1 week of preoperative intervention and assessment of healing outcome after specified elective surgical procedures were included. Randomized controlled trials with a dropout rate greater than 40% were excluded.

OUTCOME MEASURES

The outcome measures included all types of adverse healing events after surgical procedures with access through a skin incision. Short-term (necrosis of wound and tissue flaps, healing delay and dehiscence of wounds and sutured tissue, surgical site infections, and nonspecified wound complications) and long-term healing outcomes (hernias and lack of fistula or bone healing) were accessed.

DATA EXTRACTION AND STUDY EVALUATION

Data from the cohort studies and RCTs were extracted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology)[4] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[5] statements, respectively. The methodological quality of the cohort studies was evaluated in a domain-based evaluation process and by the Newcastle-Ottawa Scale, which is a scoring checklist assigning points (maximum, 9 stars) for patient selection characteristics, exposure ascertainment, comparability, and outcome assessment.[6] The methodological quality of the RCTs, including risk of bias assessment, was assessed according to Cochrane Collaboration

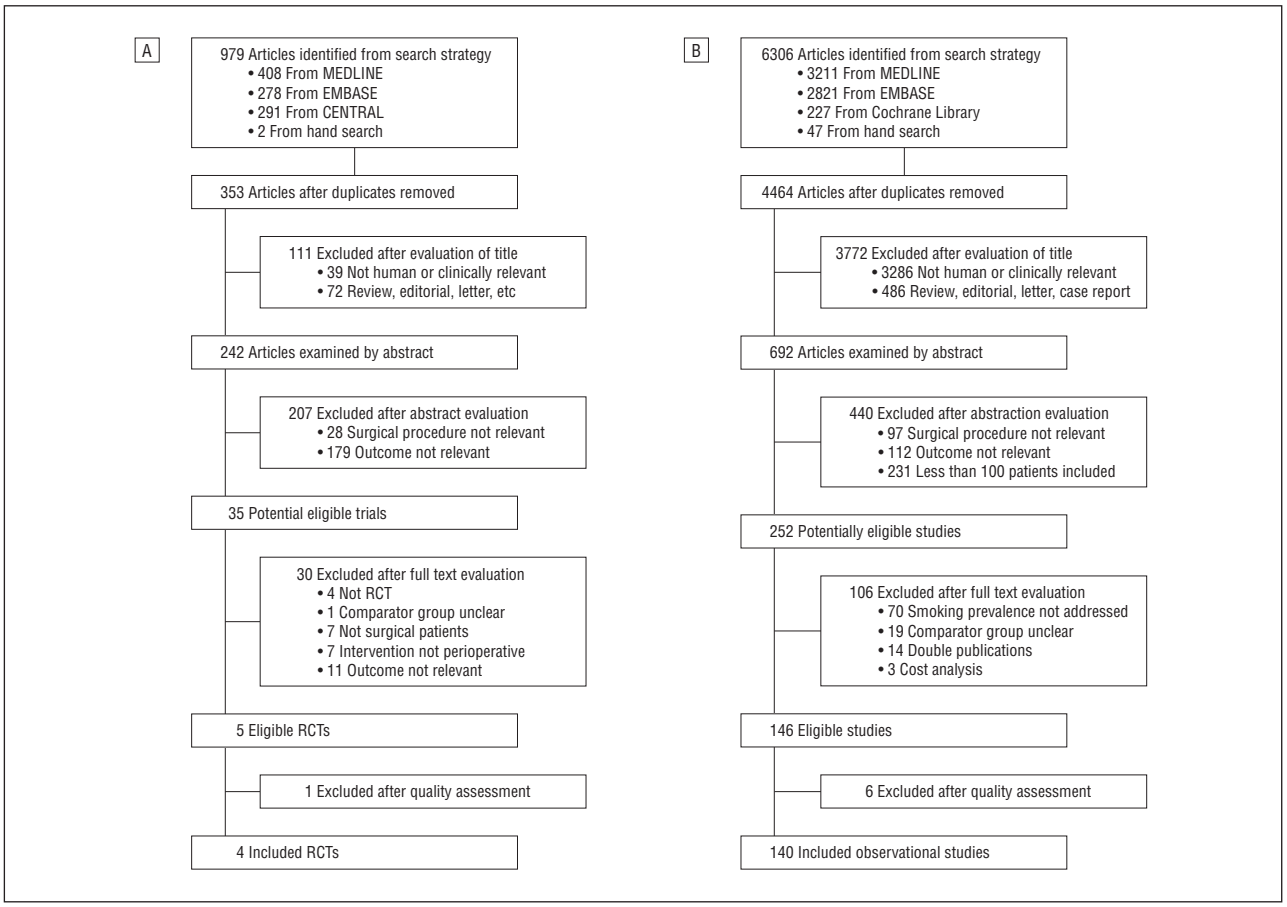

Figure 1. Flowcharts for study selection. A, Randomized controlled trial (RCT) selection. B, Observational study selection.

recommendations[7] and the Jadad score[8] for consideration of random sequence generation, allocation concealment, blinding procedures, address of incomplete outcome data, and unselective reporting. Publication bias was assessed by inspection of funnel plots calculated from meta-analyses including more than 10 studies.[7]

DATA ANALYSIS

From each study crude incidence rates or adjusted odds ratios (ORs) were extracted. Based on these data, unadjusted and adjusted estimates were calculated by means of the Mantel-Haenszel and inverse variance methods, respectively. These estimates were included in separate meta-analyses of the cohort studies according to each type of healing complication measure (smokers compared with nonsmokers) and a combined healing complication measure (former smokers compared with patients who never smoked or current smokers). Unadjusted estimates were included in the meta-analysis of RCTs.

Sensitivity analyses were conducted across complication type and included cohort studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients. Because most of the RCTs assessed outcome by pooling healing complications, sensitivity analyses aimed to estimate the impact of perioperative smoking cessation on different types of healing complications.

The statistical heterogeneity of the studies was reported as an I^2 value in each meta-analysis. Different methods of analysis were applied to assess the pooled treatment effects. In the meta-analyses of cohort studies, the random-effects model was used irrespective of the I^2 value. In the analysis of RCTs, the fixed-effects model was applied in case of an I^2 value of less than 40%.[7] The statistical analysis was performed with the use of the R program meta-analysis package, version 1.6-0.[9] In all analyses, a threshold of $P \leq .05$ was considered statistically significant.

RESULTS

The search for relevant studies yielded 6306 citations for cohort studies and 979 citations for RCTs (**Figure 1**).

CHARACTERISTICS OF COHORT STUDIES

One hundred forty cohort studies compared smokers and nonsmokers. The total number of patients included was 479 150. The studies originated from countries all over the world and embraced operations from all surgical specialties.

Twenty-six cohort studies assessed healing complications in former smokers. In 18 of these studies, former smokers were compared with current smokers and patients who never smoked. The studies originated from multiple countries and embraced general, thoracic, orthopedic, and plastic and reconstructive surgery. Half the studies defined former smokers as being abstinent from smoking for a median of 4 (range, 2-52) weeks before surgery,[10-21] whereas the other half did not address the period of preoperative abstinence.[22-35] In 2 studies, smok-

Table 2. Meta-analyses of Observational Studies on Healing Complications in Smokers Compared With Nonsmokers

Complication Category	Studies Reporting Crude Data			Studies Reporting Adjusted Values			eTable No.
	No. of Studies[a]	OR (95% CI)[b]	*P* Value	No. of Studies[a]	OR (95% CI)[b]	*P* Value	
Necrosis of wound and tissue	15	3.61 (2.78-4.68)	<.001	9	3.60 (2.62-4.93)	<.001	1
Healing delay and dehiscence	9	2.86 (1.49-5.49)	.002	12	2.07 (1.53-2.81)	<.001	2
Surgical site infection	25	2.12 (1.56-2.88)	<.001	32	1.79 (1.57-2.04)	<.001	3
Wound complications, nonspecified	20	2.06 (1.60-2.65)	<.001	17	2.27 (1.82-2.84)	<.001	4
Hernia	2	2.21 (0.71-6.84)	.17	7	2.07 (1.23-3.47)	.006	5
Lack of healing	6	2.21 (1.60-3.05)	<.001	4	2.44 (1.66-3.58)	<.001	6
Sensitivity analysis[c]	...	...	...	24	1.52 (1.36-1.69)	<.001	...

Abbreviations: ellipses, not applicable; OR, odds ratio.
[a] Indicates combined studies.
[b] Pooled treatment effects (OR [95% CI]) are calculated by means of the random-effects model. Forest plots and funnel plots on the meta-analysis and sensitivity analysis can be obtained from the author by request.
[c] Includes studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients (smokers and nonsmokers).

ers were requested to quit smoking 4 weeks before the operation and then were compared with current smokers and patients who never smoked.[19,21]

CHARACTERISTICS OF RCTs

Four RCTs assessed the impact of perioperative smoking cessation intervention. The trials originated from Denmark and Sweden.[36-39] The operations were elective orthopedic operations (hip and knee arthroplasty) and general surgical operations (herniotomy, cholecystectomy, and colorectal resection). The studies complied with the similar criteria for inclusion (ie, daily smoking, patients older than 18 years) and exclusion (ie, alcohol or other drug abuse, dementia, and lack of language proficiency). All studies reported the number of eligible patients, accounted for missing data, and discarded data from dropouts from the intention-to-treat analyses.

The intervention periods ranged from 2 to 3 weeks to 6 to 8 weeks before surgery until the day of skin suture removal or 30 days after surgery. Apart from 1 study,[37] the intervention was tailored individually and offered by study nurses professionally trained in smoking cessation therapy. The intensity ranged from brief advice with a follow-up telephone or outpatient reminder to multiple sessions of individual face-to-face counseling and unlimited hotline service access. Free-of-charge nicotine replacement drugs were offered by all but 1 study.[37] The control interventions ranged from standard advice about smoking and surgical outcome to a request to maintain daily smoking habits during the perioperative period.[38]

All studies assessed self-reported smoking or abstinence at the day before surgery and at the day of outcome assessment. Biochemical validation was assessed by measurement of cotinine levels in saliva or carbon monoxide levels in expired air. Compliance to abstinence varied from 23% to 64%.

ASSESSMENT OF RISK OF BIAS

The clinical heterogeneity was considerable in the cohort studies, and a variety of methodological flaws were present across studies. These flaws included retrospective data collection, no report of missing data, detection bias due to inadequate outcome definition, attrition bias due to inadequate postdischarge follow-up reporting, and inadequate confounder control. All RCTs had a low risk of bias, and they achieved a maximum Jadad score.

Inspection of funnel plot symmetry disclosed that the publication bias of the cohort studies was generally low (data not shown). In the cohort studies assessing surgical site infection and wound complications, a discrepancy was found between studies reporting crude incidence rates and adjusted ORs, indicating that some degree of publication bias was present in these studies.

SHORT-TERM HEALING COMPLICATIONS

Necrosis of wounds and tissue flaps was assessed in 19 unique studies including 7616 (number of subjects per study, 111-1177) smokers and nonsmokers (eTable 1; http://www.archsurg.com). Both meta-analyses disclosed a significantly higher incidence of necrosis in smokers (crude OR, 3.61 [95% CI, 2.78-4.68]) and adjusted OR, 3.60 [95% CI, 2.62-4.93]) (**Table 2**).

Most of the studies were conducted in patients undergoing breast surgery. Wound necrosis after mastectomy was 4-fold more frequent in smokers.[40,41] Three studies assessing a dose-effect relationship between the intensity of smoking and necrosis found conflicting results.[13,20,42] Two studies reported a dose-effect relationship between lifelong smoking intensity (in pack-years) and necrosis.[17,43]

In breast reconstructive surgery ranging from breast reduction to postmastectomy reconstruction, all studies demonstrated a high incidence of necrotic complications.[13,44-50] Small retrospective studies of flap transposition or free-flap reconstruction after head and neck surgery found conflicting results.[35,51-53] After lung cancer surgery and pelvic organ prolapse repair, fistulas caused by necrotic suture or mesh erosion were more frequent in smokers.[17,43,54,55]

Healing delay and dehiscence of wounds and tissue were assessed in 18 unique studies including 26 297 (number of subjects per study, 111-24 192) smokers and

Table 3. Meta-analyses of Observational Studies on Healing Complications in Former Smokers Compared With Patients Who Never Smoked or Smokers

Healing Complications Combined	Studies Reporting Crude Data			Studies Reporting Adjusted Values			eTable No.
	No. of Studies[a]	OR (95% CI)[b]	*P* Value	No. of Studies[a]	OR (95% CI)[b]	*P* Value	
Former smokers compared with those who never smoked	22	1.30 (1.07-1.59)	<.001	15	1.31 (1.10-1.56)	.006	7
Former smokers compared with current smokers	26	0.69 (0.56-0.85)	.002	2	0.28 (0.12-0.72)	.008	8
Sensitivity analysis[c]	. . .	. . .	. . .	5	1.23 (0.99-1.51)	.06	. . .

Abbreviations: ellipses, not applicable; OR, odds ratio.
[a] Indicates combined studies.
[b] Pooled treatment effects (OR [95% CI]) are calculated by means of the random-effects model. Forest plots and funnel plots on the meta-analysis and sensitivity analysis can be obtained from the author by request.
[c] Includes studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients (former smokers and those who never smoked).

nonsmokers (eTable 2). Both meta-analyses disclosed a significantly higher incidence of healing delay and dehiscence of wounds and tissue in smokers (crude OR, 2.86 [95% CI, 1.49-5.49] and adjusted OR, 2.07 [95% CI, 1.53-2.81]) (Table 2).

Most studies assessing dehiscence of wounds, fascia, and sutured tissue, including anastomotic leakage, found a higher incidence in smokers.[24,26,56-63] Postoperative healing delay as an outcome measure was assessed in a few older cohort studies. In orthopedic surgery, the reamputation rate owing to failed healing showed conflicting results[34,64-66]; in breast reconstructive surgery, more recent studies did not find postoperative healing delay to be more frequent in smokers.[16,67]

Surgical site infection was assessed in 51 unique studies including 408 428 (number of subjects per study, 100-163 824) smokers and nonsmokers (eTable 3). Both meta-analyses disclosed significantly more surgical site infections in smokers (crude OR, 2.12 [95% CI, 1.56-2.88] and adjusted OR, 1.79 [95% CI, 1.57-2.04]) (Table 2).

In general surgery, most of the studies found a higher surgical site infection in smokers.* In 1 study,[80] smokers had more surgical site infections after intestinal and colon surgery, but not after gastrectomy. After coronary bypass surgery, sternal wound infection after coronary bypass surgery was more frequent in smokers compared with nonsmokers in most studies.[10-12,33,81-92] In orthopedic and reconstructive surgery, all major studies found surgical site infection to be more frequent in smokers,[13,16,29,44,46,66,93-95] contrary to a few small studies.[96-98] In gynecologic and obstetric surgery, conflicting results were found.[99-101]

Wound complications (nonspecified) were assessed in 31 unique studies including 22 516 (number of subjects per study, 102-6676) smokers and nonsmokers (eTable 4). Both meta-analyses disclosed significantly more wound complications in smokers (crude OR, 2.06 [95% CI, 1.60-2.65] and adjusted OR, 2.27 [95% CI, 1.82-2.84]) (Table 2).

All major studies in breast reconstructive surgery found smoking to predict wound complications.[13,19,20,102,103] A number of smaller studies assessing wound complications after reconstructive surgery showed conflicting results.† Similar conflicting results were found in larger and smaller cohort studies after orthopedic, obstetric, gastrointestinal tract, and head and neck surgery.[23,25,94,118-124]

LONG-TERM HEALING COMPLICATIONS

Incisional or recurrent inguinal hernia was assessed in 9 unique studies including 2296 (number of subjects per study, 114-544) smokers and nonsmokers (eTable 5). The meta-analysis from studies[30,125-130] reporting adjusted estimates found hernia to be more frequent in smokers (OR, 2.07 [95% CI, 1.23-3.47]), contrary to the meta-analysis based on studies[27,131] reporting crude incidence rates (OR, 2.21 [95% CI, 0.71-6.84]) (Table 2).

In general surgery and urology, most studies found hernia to be more frequent in smokers,[27,30,127,130] contrary to studies of aortic reconstructive surgery, which showed conflicting results.[125,126,128,129,131]

Lack of fistula and bone healing was assessed in 10 unique studies including 14 293 (number of subjects per study, 105-12 297) smokers and nonsmokers (eTable 6). Both meta-analyses disclosed a significantly higher incidence of lack of fistula and bone healing in smokers (crude OR, 2.21 [95% CI, 1.60-3.05] and adjusted OR, 2.44 [95% CI, 1.66-3.58]) (Table 2).

In a study of open tibial fracture repair, Adams et al[132] found that smokers' fractures healed slower. All studies assessing long-term outcome after spinal surgery, except one,[133] found failed bone union to be more frequent in smokers.[21,31,134-136] In addition, unhealed sternocutaneous fistula and anal fistula were more frequent in smokers.[137,138]

HEALING COMPLICATIONS IN FORMER SMOKERS

Twenty-four unique studies reporting the outcome of 47 764 (number of subjects per study, 177-10 897) former smokers and patients who never smoked were included (eTable 7). Both meta-analyses disclosed significantly more combined healing complications in former

References 18, 27, 28, 32, 42, 60, 63, 68-79.

†*References 15, 16, 19, 45, 67, 102, 104-117.*

Table 4. Randomized Controlled Trials Assessing the Effect of Preoperative Smoking Cessation Intervention on Postoperative Healing Complications

Source/ Country	No. of Patients Included/ Completed	Intervention (Control)	Duration	Intensity	Abstinence Validation	Operation	Healing Outcome	No./Total No. (%) With Outcome	Jadad Score
Lindström et al,[36] 2008/Sweden	117/102	Nurse provided counseling, weekly FU, NRT offer, telephone hotline, and inpatient contacts (standard care)	4 wk before surgery through 4 wk after	Intermediate	Measurement of CO levels	Herniotomy, cholecystectomy, hip, or knee Arthroplasty	Wound complication	Intervention, 6/48 (13); control, 14/54 (26); $P > .05$; OR, 0.48 (95% CI, 0.2-1.2)	6
Møller et al,[39] 2002/Denmark	120/108	Nurse provided counseling, weekly FU, NRT offer, and inpatient contacts (standard care)	6-8 wk before surgery through 10 d after	High	Measurement of CO levels	Hip or knee Arthroplasty	Wound complication	Intervention, 3/56 (5); control, 16/52 (31); $P < .001$; RR, 0.16 (95% CI, 0.05-0.52)	6
Sørensen and Jørgensen,[38] 2003/Denmark	60/57	Surgeon provided counseling, telephone contacts with nurse, NRT offer, and inpatient contacts (standard care)	2-3 wk before surgery through 10 d after	Intermediate	Measurement of CO and cotinine levels	Colorectal resection	SSI, wound or fascial dehiscence, anastomotic leakage	Intervention, 9/27 (33); control, 8/30 (27); $P > .05$	6
Sørensen et al,[37] 2007/Denmark	180/149	Surgeon provided advice, counseling by telephone or outpatient talk with nurse, and NRT sample (surgeon provided advice)	4 wk before surgery through 10 d after	Low	Measurement of CO and cotinine levels	Inguinal or incisional herniotomy	SSI	Intervention, 6/101 (6); control, 4/48 (8); $P > .05$	6

Abbreviations: CO, carbon monoxide; FU, follow-up; NRT, nicotine replacement therapy; OR, odds ratio; RR, relative risk; SSI, surgical site infection.

smokers than in those who never smoked (crude OR, 1.30 [95% CI, 1.07-1.59] and adjusted OR, 1.31 [95% CI, 1.10-1.56]) (**Table 3**).

Twenty unique studies reporting the outcome of 40 629 (number of subjects per study, 177-10 897) former smokers and current smokers were included (eTable 8). Both meta-analyses disclosed significantly fewer healing complications in former smokers than in current smokers (crude OR, 0.69 [95% CI, 0.56-0.85]; adjusted OR, 0.28 [95% CI, 0.12-0.72]) (Table 3). Some of these studies assessed the effect of pack-years on healing complications in former smokers, but the results were conflicting.[13,17,20,23,25,32]

SENSITIVITY ANALYSES OF COHORT STUDIES

The sensitivity analyses confirmed that smokers had significantly more healing complications than did nonsmokers across complication types (Table 2), contrary to former smokers compared with patients who never smoked, which disclosed a nonsignificant trend (Table 3).

IMPACT OF SMOKING CESSATION ON HEALING COMPLICATIONS

Four RCTs reporting the outcome of 416 patients (number of subjects per study, 57-149) were included and healing complications were found in 15.9% (66 of 416) (**Table 4**). The meta-analysis disclosed that perioperative smoking cessation did not significantly reduce healing complications combined (**Figure 2**). In contrast, surgical site infections were significantly reduced by perioperative smoking cessation as shown by a sensitivity analysis (**Figure 3**).

COMMENT

This systematic review shows that smokers compared with nonsmokers and former smokers compared with those who never smoked have more postoperative healing complications. Former smokers (compared with current smokers) have fewer healing complications. Perioperative smoking cessation reduces surgical site infections, but not other healing complications.

Across cohort studies, necrosis was 4 times more frequent in smokers than nonsmokers, whereas surgical site infection, dehiscence, healing delay, hernia, and lack of fistula and bone healing occurred 2 times more frequently in smokers. The following pathophysiological mechanisms for defective healing in smokers appear to be involved: (1) an acute detrimental vasoactive effect of smoking leads to postoperative necrosis in tissues with fragile blood supply, such as reconstructive tissue flaps and colorectal anastomoses; (2) attenuation

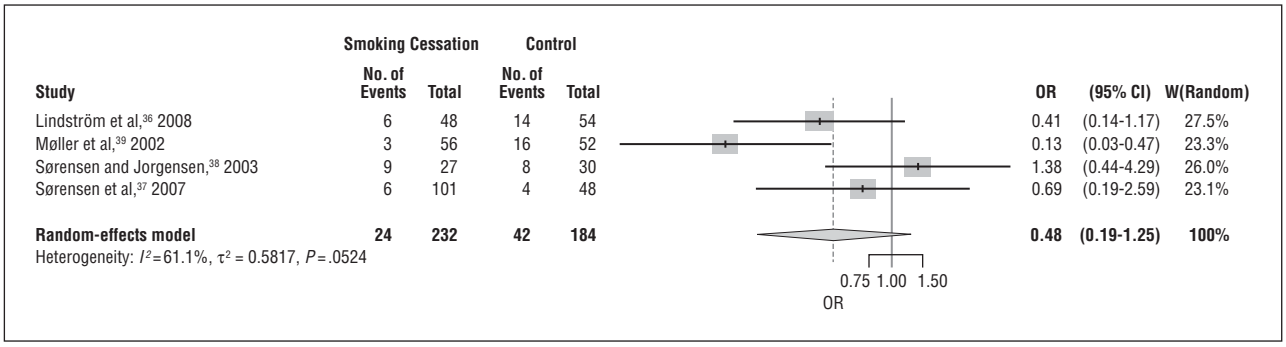

Figure 2. Meta-analysis of the effect of perioperative smoking cessation intervention on postoperative healing complications. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. OR indicates odds ratio; W, weighted.

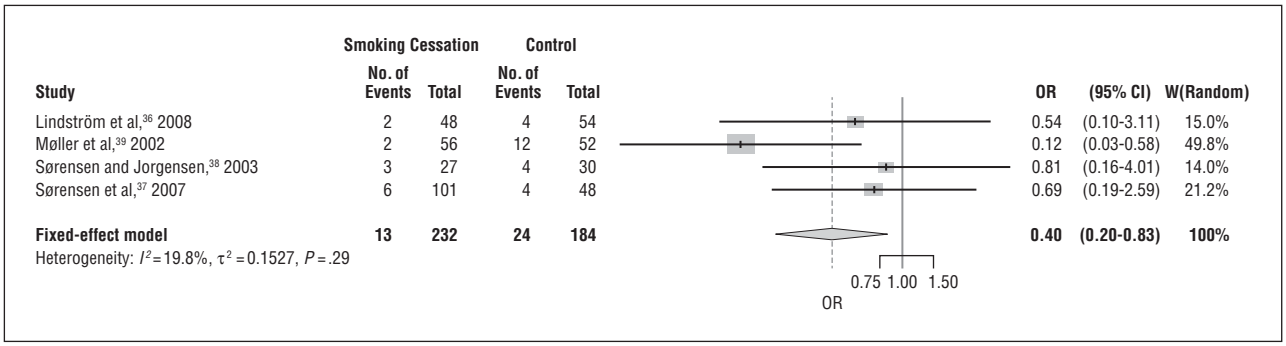

Figure 3. Meta-analysis (sensitivity analysis) of the effect of perioperative smoking cessation intervention on surgical site infection. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models. OR indicates odds ratio; W, weighted.

of the inflammatory healing response and impairment of oxidative bacterial killing mechanisms lead to surgical site infection; and (3) delay of the proliferative healing response and alteration of collagen metabolism lead to dehiscence, incisional hernia, and lack of fistula or bone healing.[139-144]

Former smokers had a one-third higher incidence of healing complications than did patients who never smoked, although the sensitivity analysis did not confirm the significance of this finding. The difference in complication rate probably reflects a sustained detrimental effect of previous smoking on postoperative healing, implying that former smokers seem to have a lifelong higher risk of healing complications than those who never smoked. The lower incidence of complications in former smokers compared with current smokers suggests that a beneficial effect of abstinence from smoking on healing mechanisms exists. The finding, however, should be interpreted carefully owing to methodological flaws and bias in the cohort studies.

The meta-analysis of the RCTs disclosed that perioperative smoking cessation intervention did not reduce pooled healing complications. This finding contrasts with 2 recent meta-analyses that disclosed that smoking cessation reduced postoperative complications overall.[2,3] Most likely the reason is methodological because 3 of the 4 RCTs included clinically heterogeneous adverse healing events in a pooled healing complication measure.[36,38,39] Wound hematomas, seromas, and subfascial collections after hip and knee arthroplasty were included as healing outcome, although none of these complications have been individually proven to be associated with smoking.[13,145]

Perioperative smoking cessation intervention including 4 to 8 weeks of preoperative abstinence from smoking significantly reduced surgical site infections. This finding suggests that the primary impact of smoking cessation on healing is a reduction in infectious healing complications as shown by Møller et al.[39] This finding was confirmed by a randomized study of healthy volunteers, which disclosed that 4 weeks of abstinence from smoking significantly reduced incisional wound infection.[146] However, in 2 of the included RCTs, 4 weeks of preoperative abstinence did not reduce surgical site infections significantly, most probably because the RCTs were underpowered.[36,37] In one of the RCTs, 2 to 3 weeks of preoperative abstinence did not affect healing complications.[38]

This is the first systematic review to examine the impact of smoking and smoking cessation on healing complications. Strengths of this methodological approach include an extensive search complying with validated search strategies and a systematic scoring of methodological quality and risk of bias assessment. The following limitations are related to methodological issues of the cohort studies: differences in design, inconsistent definitions of smoking, underreporting of smoking habits and lack of biochemical validation, inconsistent definitions of healing outcome, and unclear outcome assessment and follow-up. In addition, the lack of addressing missing data, including former smokers' recall bias for the exact time of smoking cessation, and conflicting clinical confounders to be considered restrict the validity of the cohort studies.[147-150] Although homogeneous and with a low risk of bias, the included RCTs

were small. Apart from 1 study[37] that studied healing complications as a secondary outcome measure, the actual patient number included in the other RCTs appeared to be smaller than that specified in the protocol. Consequently, the included RCTs seem to have been underpowered to show a difference in healing complications by smoking cessation.

CONCLUSIONS

Smokers have a higher incidence of infectious and noninfectious healing complications after surgery compared with nonsmokers across all surgical specialties. Former smokers appear to have a lifetime higher risk of healing complications compared with patients who never smoked. Smoking cessation for at least 4 weeks before surgery reduces surgical site infections, but not other healing complications. Patients should be encouraged to stop smoking at least 4 weeks before surgery to reduce the risk of surgical site infections.

Further cohort studies are needed to clarify the risk of former smokers for postoperative healing complications. Accordingly, valid data from a detailed smoking history including the period of abstinence from smoking should be included in future clinical database studies on surgical outcome.

Additional RCTs assessing the impact of perioperative smoking cessation on healing outcome are needed for definite confirmation. Because interventions on lifestyle changes afford a number of challenges, multicenter and large-scale RCTs using cluster randomization should be considered.

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Online-Only Material: The eTables and eReferences are available at http://www.archsurg.com.
Additional Information: Forest plots and funnel plots on cohort studies can be obtained from the author by request.
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INVITED CRITIQUE

Kicking Society's Tobacco Habit

Does the Butt Stop Here?

An astonishing 1 in 5 US adults are current smokers (≥100 lifetime cigarettes and regular consumption).[1] Although this figure has declined a little recently, the overhanging health issues will persist for some time. The current findings of adverse effects on surgical site infections and reparative processes are less surprising.[2] However, can we confidently determine inhaled tobacco smoke as an isolated risk factor with the current study design? There are far too many covariables to digest. Smokers tend to be in lower socioeconomic groups, be more sedentary, drink more alcohol, and have more comorbidities than current nonsmokers (ex-smokers) and never (life-long tobacco-free) smokers. The inadequate power of the studies, the well-recognized inaccuracy with which patients report their smoking habits, and the haziness of wound-healing definition (eg, rate of healing, time to complete closure, patient satisfaction, self-assessed or surgical scores?) are prohibitive impediments to present data interpretation and the call for future trials.

A more pragmatic position for the surgical community to maintain is a consistent antitobacco attitude, encouraging and strongly recommending cessation (whether or not it is in advance of an operation). This moral imperative helps reduce direct and related health care costs and so benefits the patient and society as a whole. Sustained comprehensive tobacco control programs that include patient information, support programs, health warnings, media campaigns, and smoke-free policies work. California, Washington, Maine, and New York saw their smoking prevalence fall by 40% or more in the past decade by implementing these programs. The question is not at what cost this is achieved. Federal and state government must support health care reform that embraces tobacco control or risk being the butt of society's smoke.

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Review

OXFORD

Review

NIH Electronic Cigarette Workshop: Developing a Research Agenda

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Abstract

Background: Electronic cigarettes (e-cigarettes) represent an emerging public health issue. These devices deliver nicotine along with other constituents, including flavorants, via an inhalable aerosol. Their uptake is rapidly increasing in both adults and youths, primarily among current smokers. Public debate is increasing on how these devices should be regulated and used, yet only limited peer-reviewed research exists. To develop a informed policy for e-cigarettes, their effects on human behavior, physiology, and health need to be understood.

Purpose: This paper describes proceedings from a National Institutes of Health–sponsored workshop, which was held in November 2013, to identify research needs related to the effects of

e-cigarettes. Discussion topics included e-cigarette risks and abuse potential; the potential role for e-cigarettes in harm reduction and smoking cessation; unintended consequences of e-cigarette use, such as becoming a gateway to conventional cigarettes; and dual use of both e-cigarettes and conventional cigarettes.

Results and Conclusions: The research needs identified by the workshop participants included the following: standards to measure the contents and emissions of e-cigarettes; biomarkers of exposure; physiological effects of e-cigarettes on tissues and organ systems, including pulmonary and cardiovascular; information on e-cigarette users, how the devices are used, and identification of the best tools to assess these measures; factors that drive use and influence patterns of use; and appropriate methods for evaluating a potential role for e-cigarettes in smoking or nicotine cessation. To understand fully the challenges and the opportunities that e-cigarettes represent, expertise will be needed in basic, behavioral, translational, and clinical sciences.

Introduction

Electronic cigarettes (e-cigarettes), a type of electronic nicotine delivery system, represent a dramatic new nicotine delivery technology. These devices can deliver nicotine along with other constituents via an aerosol, which is then inhaled, mimicking the feel of a conventional cigarette. This may serve to satisfy many of the behavioral and sensory cues of smoking in addition to providing nicotine. Introduced in the United States in 2007, e-cigarettes sales have been doubling annually and by 2013 were projected to become a nearly $2 billion industry.[1,2] This rapid uptake suggests e-cigarettes are a disruptive innovation to the conventional cigarette market. They may represent a less risky alternative to conventional cigarettes because users are not exposed to carbon monoxide (CO) or other toxicants at the same levels produced by the combustion of tobacco as in conventional cigarettes. However, the consequences of long-term exposure to the constituents of e-cigarettes remain unknown.

Data on the effects of e-cigarettes on human physiology and health are limited in part due to their recent emergence as well as their rapidly evolving construction and lack of standardization.[3–5] Currently in the United States, the devices are largely unregulated at the federal level. Although some jurisdictions in the United States have laws prohibiting use in some public places and prohibiting sales to minors, the US Food and Drug Administration (FDA) currently does not have the authority to regulate e-cigarettes as tobacco products. A rule was proposed in April 2014 to extend the FDA's "tobacco product" authorities (which currently only apply to conventional cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco) to additional categories of tobacco products that meet the statutory definition of "tobacco product," including e-cigarettes (www.regulations.gov/#!documentDetail;D=FDA-2014-N-0189-0001).

Given the increasing popularity of e-cigarettes and their potential impact on the use of conventional cigarettes, the health science community must understand the effects of e-cigarettes on human health, how they affect nicotine addiction, and their potential role in smoking cessation and replacing combustible tobacco.

The National Institutes of Health (NIH) in 2013 sponsored an e-cigarette workshop to inform and promote research in this area. The goal was to facilitate interaction among investigators experienced in working with conventional and e-cigarettes and to discuss the need for a broad research perspective that should include tobacco use, nicotine addiction, biomarkers, harm reduction, epidemiology, and smoking cessation. Although not intended to be all-inclusive, this workshop represented an effort to identify many of the important research gaps.

The workshop focused on device design and characteristics, delivery of nicotine and other constituents, physiological consequences of exposure, patterns of e-cigarette use and issues associated with designing clinical studies to evaluate e-cigarette use in harm reduction and smoking cessation. These topics were further divided into subsections, presented below. In addition, regulatory perspectives were provided by representatives from the FDA Center for Tobacco Products (CTP) and the FDA Center for Drug Evaluation and Research (CDER).

E-Cigarette Design and E-Liquid Constituents

A typical e-cigarette consists of a battery, a reservoir containing e-liquid (usually a mixture of propylene glycol, glycerol, nicotine, flavorants, and other additives), a microprocessor, an air flow sensor or activating button, and a heating element. The heating element is usually a wire or rod made from various metals (e.g., nickel, chromium, copper coated with silver). In many devices, when a user takes a "puff," an air flow sensor activates the flow of electricity to the heating element, which heats and aerosolizes some of the e-liquid. This aerosol is analogous to the mainstream smoke from a conventional cigarette.[6] Numerous e-cigarette designs are currently on the market with new ones rapidly becoming available. The original e-cigarette design, often called "cigalikes," resemble conventional cigarettes. Newer, larger devices often referred to as "tank systems" or "personal vaporizers," deliver nicotine more effectively and are increasingly popular.[2,3] Tank systems have larger e-liquid reservoirs, larger batteries, and often bear no resemblance to a conventional cigarette. Because voltage affects delivery of nicotine (and other e-liquid constituents) to the aerosol, many devices now incorporate a tunable voltage battery.[2,7,8] Users can adjust, or "tune," the voltage to optimize the amount of nicotine in each puff. Other customizable features that may result in higher concentrations of nicotine or other constituents in the aerosol include dual coil atomizers and multiple chamber atomizers.[6]

The chemical composition of the e-liquids varies considerably from brand to brand.[9] In most products, nicotine is dissolved in mixtures containing propylene glycol and/or glycerol. Although some manufacturers indicate use of current Good Manufacturing Practices to generate their e-liquids, no standards are mandated. E-cigarettes may contain undisclosed additives and new formulations are continually introduced into the market. US regulation bans conventional cigarettes with characterizing flavors (not including menthol), such as pineapple, chocolate, and cherry.[10] It is important to note that younger smokers exhibited a preference for flavored cigarettes.[11]

E-cigarettes are often sold in flavored varieties including fruit and candy flavors and, in a similar manner, the flavors may preferentially increase the product's appeal to younger smokers. Other additives may include ethyl alcohol, stabilizers, and non-nicotine pharmacologically active compounds.

Aerosol Generation and Constituents

A key aspect of e-cigarette function is its ability to deliver nicotine from the e-liquid to an inhalable aerosol, popularly called vapor.[12] Smoking machine technology, developed for quantifying combustible tobacco smoke toxicant yield, can potentially be used with e-cigarettes to generate aerosols for analysis. Nicotine yield in the aerosol is influenced by multiple factors, including the way air flows through the device, puff volume, and puff duration (i.e., the "puff topography").[6,7,13] The correlation between experimental product emissions and what is generated by the user is high when machine puffing exactly mimics human behavior.[14] However, accurate data on puff topography are required. For example, current e-cigarettes generally deliver less nicotine per puff than conventional cigarettes.[4,15] Because an e-cigarette can contain up to 40 times more nicotine than a conventional cigarette, the user can compensate for the decreased nicotine per puff by employing a different frequency, depth, and intensity of puffing to obtain more nicotine. Understanding the topography will allow accurate characterization of the devices.

Analyses of the aerosols from several brands of e-cigarettes revealed differences in their efficacy and consistency of nicotine aerosolization.[4,9] This is likely to result from differences in device design, including heating elements, cartridge size, and battery strength. An empirically derived mathematical model is under development that may aid in understanding how these differences affect the amount of nicotine in the aerosol.[7] Studies are also needed to explore how the puffing behavior is influenced by nicotine levels in an aerosol, sensory effects of nicotine and aerosol constituents (e.g., so-called "throat-impact"), taste and flavor of inhaled aerosol, and efficacy and speed of nicotine delivery to the bloodstream and brain to alleviate cravings. These characteristics modulate how smokers use conventional cigarettes, and e-cigarette users are likely to be similarly affected.[16,17]

In addition to characterizing the aerosol nicotine concentration, the identities and concentrations of other aerosolized constituents and toxicants need to be determined. Recent studies found that though the aerosols contained some toxic and carcinogenic substances, including formaldehyde, acetaldehyde, acrolein, and traces of nitrosamines, the levels were 9–450 times lower than in conventional cigarette smoke and were often comparable with the amounts generated by a nicotine inhaler.[9,12] The levels of these substances, however, can depend on the voltage used to generate the aerosol.[8] Heavy metals have also been identified in e-cigarette aerosols.[9,18,19] Studies are needed to assess whether the levels of toxicants in e-cigarette aerosol pose a health risk and to determine their toxicity thresholds.

Nicotine bioavailability and other biomarkers of exposure need to be measured. The aerosol deposition and absorption sites in the oral cavity and respiratory tract depend to a large extent on particle size. However, tobacco smoke exhibits far greater deposition than would be predicted by particle size due to the so-called "cloud motion" interaction among the particles.[20] Although e-cigarette aerosol particles are generally similar in size to that of tobacco smoke, it is unclear if they interact in a similar manner.[21,22] Data are needed on the sites of e-cigarette aerosol deposition, the route of absorption, and the relationship between the concentration of nicotine in the aerosol and the rate of uptake to the blood stream.

Secondhand and Thirdhand Exposure to Aerosol Constituents

Although e-cigarettes do not generate sidestream aerosol emissions, secondhand mainstream aerosol exhaled by the e-cigarette user may involuntarily expose nonusers to the nicotine, ultrafine particles, volatile organic compounds, and other constituents released with exhaled aerosol.[18,23–25] Substances remaining on the surfaces in areas where people have used e-cigarettes may contribute to thirdhand exposure. For example, studies show nicotine from tobacco smoke can react with oxidizing chemicals in the air to form secondary pollutants, such as carcinogenic nitrosamines.[26] This reaction may also occur with nicotine from e-cigarette aerosol. Research is needed to evaluate the level of exposure and health consequences of secondhand and thirdhand exposure to the constituents in e-cigarette aerosol, especially among vulnerable populations, including children and pregnant women.

Unintended Uses of E-Cigarettes

There is a potential for e-cigarettes to be misused, either by altering how they interact with nicotine liquids or by using the devices to deliver drugs other than nicotine. One reported method of altering the nicotine delivery characteristics is via "dripping," that is, placing drops of the e-liquid directly onto the heater.[27] Dripping can produce increased levels of nicotine and volatile aldehydes in the resulting aerosol because the heating element can reach a higher-than-intended temperature when not submerged fully in liquid.[6,7,28] E-cigarettes may also be used with drugs other than nicotine, such as marijuana extracts.[29–31]

Abuse Liability: Nicotine

The risk that the use of a drug containing product will lead to addiction is often referred to as it's "addiction sustaining liability," "abuse potential," or "abuse liability."[32,33] The abuse liability of a given drug can be greatly influenced by the design of the product's dosing characteristics including speed of delivery and absorption, and other factors that contribute to the ease, pleasure, and attractiveness of use of the product.[32,34,35]

Nicotine delivery by e-cigarettes has gained the attention of some tobacco smokers as a means to decrease their exposure to the toxicants from combustible tobacco. However, there is a potential health risk for individuals who are not current tobacco users and may become dependent on nicotine via e-cigarettes. These individuals may be former smokers who relapse or nonsmokers who use nicotine for the first time. Rapid arterial absorption of nicotine via the lungs following inhalation of tobacco smoke leads to a reinforcement of the effects of nicotine and is an important contributor to addiction risk or abuse liability.[36,37] In contrast, for example, products can be designed to minimize addiction risk, as with nicotine by gum or lozenge in which the delivery is buccal, and provides relatively slow and low venous exposure compared with inhaled nicotine.

Studies of early e-cigarettes indicated nicotine was absorbed at low levels, suggesting a lower risk of abuse liability than with conventional cigarettes.[3,38–40] Newer versions of e-cigarettes, however, can readily deliver higher levels of nicotine. Furthermore, e-cigarette users can modify their behavior to optimize nicotine delivery, with some able to achieve conventional cigarette-like plasma nicotine concentrations[27,41,42] Evolution in design could lead to devices that carry an equal or higher risk of abuse liability and addiction than conventional cigarettes, which may be positively related to the likelihood of uptake, continued use, and the potential to substitute for combusted tobacco.

Thus, the abuse liability of e-cigarettes needs to be assessed, both with current models and with new devices as they develop to deliver greater amounts of nicotine. As previously noted, the behavioral and sensory aspects of e-cigarettes may also play an important role in their abuse liability and these may be useful to consider when assessing the devices. A variety of methods are used to assess abuse liability of drugs, and can include measurements such as liking, craving, withdrawal, and other psychological responses.[32,40,43] Furthermore, investigations should take into account the variety of populations that may use these products. Policies and practices regarding e-cigarettes will require balancing their potential to assist adult users of conventional cigarettes to quit, with their potential to facilitate nicotine addiction among youth and adult nonsmokers, and relapse among former smokers.

Effects of Chemosensory Agents and Flavorants

Flavorants and other constituents that contribute to the chemosensory effects of a product can affect its appeal and abuse liability.[34] Agents that may have these effects, such as pyrazines, inorganic acids, and essential oils, are added to the liquids of at least some e-cigarettes.[18,44] The Merit brand conventional cigarette had pyrazines artificially added to enhance its flavor.[45,46] Consumer testing sponsored by the manufacturer of Merit, Philip Morris, found the majority of participants reported that the new Merit was equal or superior in taste to brands that delivered 60% more tar.[46,47] Merit subsequently gained a large portion of the conventional cigarette market.[46] Similar compounds, found in the "flavor" fluids of e-cigarettes, may alter the sensory and chemosensory effects of the e-cigarette aerosol in a way that increases user satisfaction.[48,49] These characteristics not only have the potential to make e-cigarettes more satisfying and promote switching from conventional cigarettes, but may also increase their abuse potential. Moreover, some of these agents were identified as potential reproductive toxicants.[50]

Evaluating Acute and Long-Term Biophysical Effects

The measures for tobacco-induced harm (particularly smoking) were designed to detect changes occurring over many years, long after initiation. The recent introduction of e-cigarettes requires measures that must also assess the acute health impact. Use of e-cigarettes can increase lung flow resistance, modulate oxidative stress, and increase heart rate and blood pressure, with some of these effects directly related to the delivery of nicotine.[40,42,51,52] However, few reports focusing on the acute effects of e-cigarettes are available, and both basic and clinical studies are needed. The majority of the e-liquid in e-cigarettes is comprised of propylene glycol and glycerol. These compounds have the designation, "Generally Regarded as Safe" as a food additive (www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm). Additionally, propylene glycol is used in some asthma inhalers. However, there is limited data available on the inhalation of either compound at the concentrations present in e-cigarettes. For glycerol-containing solutions, one concern is that when heated they can produce acrolein, a compound shown to be harmful to lung function.[53–55] Propylene glycol can cause airway irritation, eye inflammation, and nasal congestion,[56,57] and some of these effects have been reported by users of e-cigarettes.[51,58] The health effects of inhaling these constituents repeatedly throughout each day for years need to be evaluated. Relevant assessments include pulmonary, cardiovascular, and carcinogenic measures. Evaluations of associated health risks are needed to assess the potential role of e-cigarettes in harm reduction. Specifically, data are needed to evaluate both their short-term use as a smoking or nicotine cessation therapy and their longer term use as an alternative to and potentially less risky source of nicotine than combustible tobacco products.

Biomarkers of Exposure

Studies on the acute use of e-cigarettes will require urine or plasma biomarkers that can provide an objective indicator of dose. This approach is extremely useful in assessing toxicant and carcinogen exposure in people who use tobacco products.[59] Measures have yet to be identified that specifically report on e-cigarette use and would not show altered levels from dual use with conventional cigarettes. Previously described biomarkers not unique to e-cigarette use include total nicotine equivalents (sum of nicotine, cotinine, 3′-hydroxycotinine, and their glucuronides), which can be measured in urine.[60] These urinary compounds represent approximately 73%–96% of the nicotine dose and provide a superb indicator of nicotine uptake. The nicotine metabolite ratio (ratio of 3′-hydroxycotinine to cotinine) in plasma is an excellent phenotypic indicator of hepatic CYP2A6 activity in smokers and can be used as a measure of individual risk for addiction.[61]

The tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN), may provide important indicators of relative combustible tobacco and e-cigarette use, as their levels in e-cigarettes were recently shown to often be substantially lower than in combustible tobacco.[9,62] The ratio of cotinine to total NNK metabolites (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides) in urine could be a useful biomarker of dual use of combustible tobacco products and e-cigarettes as it is expected to be significantly lower in combustible tobacco product users than in e-cigarette users.[63,64] Total NNN, including its glucuronide, can be measured in urine. Although NNN is expected to be low in e-cigarette users, it can be generated in the body by nitrosation of nornicotine, which is co-extracted with the nicotine from tobacco or can be generated in vivo through nicotine metabolism.

Quantification of e-cigarette contaminant exposure is also important. 3-Hydroxypropylmercapturic acid (3-HPMA) and 2-HPMA (metabolites of acrolein and propylene oxide, respectively) can be measured. Acrolein is produced by the heating of glycerol, and propylene oxide is a potential decomposition product of propylene glycol. Additional toxic effects of e-cigarettes potentially could be assessed by measuring DNA adducts of formaldehyde and acrolein in leukocytes.[59] This suite of biomarkers has the potential to provide objective data on levels of nicotine as well as selected important carcinogens and toxicants that may be associated with e-cigarette use.

Determining Patterns of Use

Data on how e-cigarettes are being used and how they affect the prevalence of conventional cigarettes are critical for understanding the impact of these devices on public health. To fully explain the interest in these devices, it is important to know the patterns of use, the beliefs about the devices, the reasons for their use, and how these are affected by the changing marketplace. A pressing challenge is how to gather and integrate information over time to best understand the specific patterns of risk and exposures. Cross-sectional studies of e-cigarette use from 2010 to 2012 among US adults showed they were primarily being used by current smokers, with "ever use" ranging from 6.8% to 11.4% in 2010[65,66] and increasing to 32.2% in 2012.[67] This rapid uptake by current smokers could indicate their desire to find a less risky alternative to conventional cigarettes. The

perception that e-cigarettes are less harmful/toxic than conventional cigarettes is one of the most commonly cited reasons for use; other reasons include believing e-cigarettes will help reduce tobacco craving and withdrawal symptoms, wanting to reduce conventional cigarettes smoked or to quit smoking conventional cigarettes altogether, and wanting to prevent relapse to conventional cigarettes.[66–72] Use by former smokers increased from 2.5% in 2010 to 7.4% in 2011, though what fraction were recent quitters of conventional cigarettes is unknown. Use by never-smokers ranged between 1.0% and 2.0% over the years 2010–2012, with no apparent directional trend.[65–67] Additional assessments are needed to determine if this low rate will continue.

Surveillance systems and studies are needed to further understand the patterns and trajectories of use. The Population Assessment of Tobacco and Health (PATH) Study is a longitudinal study of up to 59,000 individuals, includes youths and adults and will likely provide invaluable information on e-cigarette use (www.pathstudyinfo.nih.gov). However, the PATH Study's annual data collection may make rapid assessment of e-cigarette use difficult. Monitoring the Future surveys 50,000 8th, 10th, and 12th graders and also includes questions about e-cigarettes (www.monitoringthefuture.org). This annual survey should supply key information about how the devices are being used by US youth. Nonetheless, reporting more often than annually is needed to spot trends in this rapidly changing area and to efficiently identify the populations using e-cigarettes, how they are being used, why they are being used, and under what conditions. For example, the Legacy Longitudinal Survey is bi-annual and surveys young adults 18–29 years of age. This survey recently found that among the 23% of young adult current conventional cigarette users, 30% reported dual use with other tobacco or nicotine containing products, with e-cigarettes accounting for 9% of total dual use.[73]

Dual Use

Many e-cigarette users are not exclusive users of the devices, but are "dual users," that is, users of both e-cigarettes and conventional cigarettes.[74] This suggests that rather than quitting their combustible use, the smokers instead added e-cigarettes. Although dual use can lead to substantial reductions in conventional cigarette consumption, this behavior may not confer significant reduction in harm, particularly for long-term conventional cigarette users. However, long-term dual use of nicotine replacement therapy (NRT) and conventional cigarettes does not produce significant adverse events and increases, not decreases, the motivation to stop smoking.[75,76] Mean cotinine levels of e-cigarette dual users appear to be similar to that of conventional cigarette-only users, indicating nicotine intake remains relatively constant.[77,78] Thus far, limited longitudinal data provide a conflicting picture of whether dual use is linked to consistent changes in motivation to stop conventional cigarette use.[77,79–81]

Assessments of dual use will need to be very clear about how it is characterized. Definitions that may exclude or include the very different situations of using 1 e-cigarette a week and 20 conventional cigarettes per day versus using 5 conventional cigarettes a week and e-cigarettes daily could result in very different measurements of dual use. These differing definitions will affect measurement of the prevalence and incidence of dual use, the percent of e-cigarette users who dual use, and the direction of trends in dual use.

The long-term impact of dual use is unknown. Does dual use lead to greater reductions in conventional cigarette use over time, facilitate or delay quit attempts, or alter dependence (e.g., increased dependence because of greater nicotine exposure or decreased dependence due to less rapid delivery of nicotine via e-cigarettes)? The scientific literature is also sparse on the effects of dual use on the smoking topography of usual brand cigarettes and resultant nicotine and toxicant exposures.

Youth and E-Cigarettes

The prevalence of e-cigarette use among US adolescents doubled between 2011 and 2012.[82] The percentage of high school students who reported ever use increased from 4.7% in 2011 to 10.0% in 2012 and use within the past 30 days increased from 1.5% to 2.8% over the same time. Use nearly doubled among middle school students, from 1.4% in 2011 to 2.7% in 2012. A cross-sectional survey of four high schools in Connecticut and New York indicated similar trends, with past 30-day e-cigarette use increasing from 0.9% in 2010 to 2.3% in 2011.[83] Greater than 75% of high school e-cigarette users were dual users with conventional cigarettes.[82,83] However, the increased prevalence of e-cigarette use in US youth is occurring at a time when overall smoking by teens showed a decrease, from 10.6% in 2012 to 9.6% in 2013.[85]

A primary question is whether e-cigarettes promote nicotine addiction or conventional cigarette use in youth above what would otherwise be the case if the devices did not exist, whether they would further reduce conventional cigarette use, or result in dual use. In high school, youth current smokers have the highest rate of knowledge, willingness to use, or use of e-cigarettes.[84,86–88] Although some youths who are nonsmokers also report e-cigarette ever use, estimates suggest this represents about 10% of middle and high school users.[82] There are multiple reasons for teens and young adults to become interested in using e-cigarettes, varying across age groups.[84,89–92] Focus groups of college, high school, and middle school students uniformly reported use due to curiosity and the attractiveness of flavors.[90] Among college and high school students, use of e-cigarettes by friends and family and the desire to quit smoking were motivating factors for use. Availability was also an important factor among high school students as were signs of independence among middle school students. Factors deterring initiation of e-cigarette use included smoking perceived as not cool, the expense, and their similarity to cigarettes.[84,90] When those who tried e-cigarettes were asked the reason for e-cigarette discontinuation, youth smokers noted that they were not the same as cigarettes and youth nonsmokers indicated that the novelty wore off.[84,90] An understanding of the trajectory of youth e-cigarette use, reasons for use, and consequences of use are needed.[93] Additionally, the role of flavors in the initiation and maintenance of e-cigarette use in youth, and strategies to reduce and prevent youth initiation need to be evaluated.

E-Cigarettes and Pregnant Women

Pregnant women who smoke conventional cigarettes are a population especially vulnerable to the use of e-cigarettes because of the popular view that the devices represent a less risky alternative to nicotine delivery. This is despite several studies indicating that NRT is not efficacious for smoking cessation during pregnancy.[94–97] Although some high-income countries recommend NRT for pregnant smokers when behavioral therapies have failed, other countries do not recommend NRT presumably due to lack of maternal and fetal safety and smoking cessation efficacy data.[98] However, NRT treatment did lead to increased birth weight and gestational age compared with placebo, probably due to a reduction in CO and other toxicants in tobacco smoke.[96,97] Similar to NRT, e-cigarettes do not produce CO and e-cigarette aerosols may

have reduced toxicant exposure relative to conventional cigarettes. The potential for e-cigarettes to not only deliver nicotine but also mimic the sensory aspect of smoking may be an important factor in reducing cigarette cravings in women by these devices.[99,100]

As pregnant women are considered a vulnerable population, and nicotine, CO, carcinogens, and other chemicals in tobacco are reproductive toxicants,[96] the risk/benefit profile of e-cigarettes needs to be determined in this population of smokers. Of primary interest is to characterize the prevalence rates, overall nicotine exposure, cessation outcomes, and maternal and infant health outcomes of women who use e-cigarettes during pregnancy. Short-term clinical studies examining changes in acute and overall nicotine exposure and maternal and fetal hemodynamic parameters with e-cigarettes compared with conventional cigarettes and NRT are needed prior to longer term efficacy trials. Despite the potential for e-cigarettes to be useful for cessation in this population, the safety of the constituents in e-cigarettes has yet to be fully investigated and use during pregnancy may pose additional risks to the mother and the fetus.[9,101]

Clinical Studies

Prospective clinical studies are needed to understand whether e-cigarettes have value in harm reduction by leading to a complete switch from conventional cigarettes to e-cigarettes, by reducing conventional cigarette use or by aiding in nicotine cessation. Data from the limited number of clinical trials using e-cigarettes for smoking cessation suggest no differences in abstinence rates between e-cigarettes that do or do not contain nicotine or between NRT and e-cigarettes.[77,79] However, caveats with these studies include the limited size of the samples, the use of first-generation e-cigarette products that may not have delivered nicotine effectively, and the possible use of inadequate instructions. A retrospective analysis of data from the U.K. Smoking Toolkit Study indicated that individuals using e-cigarettes to quit smoking were about 1.6-fold more successful than users of NRT with no professional support or no aid.[102] It is unknown what proportion of the e-cigarettes users who quit smoking still used the devices. Regardless, if e-cigarettes are equally effective for smoking cessation as NRT but more popular, on a population level there may be a greater overall decrease in smoking with the devices.

Several challenges and product-specific considerations are associated with e-cigarette clinical trials. For example, comparing e-cigarette trials with studies evaluating other cessation treatments may be difficult because of the differences in the marketing practices, as well as differences in the motivations of the participants for entering a trial (e.g., reducing harm by smoking fewer cigarettes, converting to long-term use of e-cigarettes, or using e-cigarettes as a means of quitting the use of all nicotine products). Additional important factors include the specific characteristics of the device used (including voltage of power supply, resistance of heater, concentration of nicotine, and nicotine delivery to the user), the sample population, the participant's perceptions of the product, and their rationale for entering the study.

Comparative effectiveness designs of nicotine cessation trials may be particularly informative for evaluating e-cigarettes. Understanding the value of the devices relative to current cessation therapeutics is needed to make informed risk/benefit analyses; trials comparing only placebo versus active treatment are less useful.

In conducting clinical trials with e-cigarettes, specific parameters need to be considered, such as the optimal duration of use and dose, which can be particularly challenging as differences in puff topography among users could lead to substantial variations in nicotine exposure. Clinical trials may require providing instructions to subjects on how to use the product, in order to standardize exposures. Additionally, the availability of e-liquids with varying nicotine concentrations suggests that trials to assess gradual nicotine reduction may be particularly suitable for these devices.[103]

Outcomes that may be especially important in determining the relative effectiveness of e-cigarettes as a smoking cessation aid would include the health effects of long-term use, patterns of dual use, nicotine and toxicant exposure biomarkers, and abstinence from combustible products. Exposure biomarkers that differentiate between e-cigarette and conventional cigarette use would be important for studies investigating a switch from combustible tobacco to e-cigarettes.

FDA Regulations and Requirements for E-Cigarettes in Clinical Studies

In 2008 and prior to the enactment of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), FDA determined that certain e-cigarettes were unapproved drug/device combination products. This determination was challenged in court. The US Court of Appeals for the D.C. Circuit ruled that e-cigarettes and other products "made or derived from tobacco" can be regulated as tobacco products and are not drugs and/or devices unless they are marketed for therapeutic purposes (*Sottera, Inc.* v. *Food & Drug Administration*, 627 F.3d 891 [D.C. Cir. 2010]).

Table 1. Key Research Gaps: Definitions and Methods

Definitions
• What should the devices be called: electronic nicotine delivery systems (ENDS, though some contain no nicotine), electronic cigarettes, e-cigarettes, aerosolized delivery system? • What is the definition of ENDS and electronic cigarettes? • How should the various types of e-cigarettes be classified? • What terms should be used when surveying consumer use, such as e-hookah or hookah pen?
Methods, populations, moderating factors
• What standardized methods should be used to assess the function and effects of e-cigarettes? –Machine-determined exposures (mimic human behaviors) –Aerosol generation and constituent evaluation –Pharmacokinetic and acute effects studies (control for volume, duration, naive vs. experienced users, etc.) –Quantification of e-cigarette use—number of cartridges, tank refills, disposable products –Quantification of dependence –Clinical trial methods and outcome measures –Animal models • What tools could be developed to understand effects? –Labeled nicotine tracer in e-cigarette liquid to assess delivery –Placebo e-cigarettes with additive (e.g., capsaicin) to mimic nicotine harshness • What are the intra- and inter-variation in user response to e-cigarettes? • What factors within populations moderate the effects of e-cigarettes? –Age –Sex –Race –Pregnancy –Vulnerable populations (low income, co-morbid mental illness or other disease, high-risk groups such as youth) –History of e-cigarette use, e.g., naive and experienced users

Currently, FDA CTP does not have regulatory authority over e-cigarettes. However, in April 2014, FDA proposed a rule, which would deem additional tobacco products to be subject to regulation under the Tobacco Control Act. If this rule is finalized, any e-cigarette that meets the legal definition of a "new tobacco product" will require a marketing authorization order from CTP. CTP may exempt a "new tobacco product" that is intended for investigational use from the Tobacco Control Act's new tobacco product provisions. CTP may also issue regulations establishing the conditions under which persons can use a tobacco product for investigational use. Investigators with questions about exemptions from new tobacco product regulations may request a meeting with CTP's Office of Science. CTP intends to develop a guidance document to clarify the process and describe CTP's current thinking about investigational tobacco products.

FDA CDER does have jurisdiction over drug products, including e-cigarettes, with therapeutic claims. In general, a study evaluating the use of e-cigarettes for a therapeutic purpose requires an investigational new drug (IND) application if it is a "clinical investigation." A "clinical investigation" is any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects (21 CFR 312.3(b)). In clinical investigations where an e-cigarette is being evaluated for a therapeutic purpose, the e-cigarette would be considered a drug/device combination product for which FDA CDER has primary regulatory jurisdiction. An IND is required for such research to assure the safety and rights of subjects in all phases of the clinical investigation and, in phases 2 and 3, to help assure that the quality of the research is adequate to permit an evaluation of the drug's effectiveness and safety (21 CFR 312.22). The applicable procedures and requirements for clinical investigations conducted under an IND are set forth in title 21 of the Code of Federal Regulations, part 312 (21 CFR 312) (the IND regulations).

Whether an IND is required for a study that involves the use of an e-cigarette by human subjects depends largely on the study's objectives. As noted previously, if the study is intended to evaluate the use of e-cigarettes for a therapeutic purpose, it is regulated by CDER as a study of a drug/device combination product and would most likely require an IND. Investigators with questions regarding whether their study protocol would require an IND can make an inquiry to FDA CDER.

Research Gaps and Key Challenges

Despite the ready availability of e-cigarettes at local stores and on the Internet, only limited published research is available and significant research gaps remain. The paucity of data is not surprising as these devices have been commercially available for less than a decade, became popular only in the last few years, and are rapidly evolving. Tables 1–3 present the key research questions raised by the workshop attendees. As described in Table 1, there is a lack of agreement on what defines the class of devices and appropriate terminology. Table 1 also presents basic research needs, which includes defining measurement standards on the performance and emissions of e-cigarettes and determining how to measure their effects using animal models. Table 2 lists research questions related to product design and constituents, health risks, addiction, and sensory appeal. These questions address gaps in knowledge surrounding technological aspects of the devices and their biochemical and physiological effects. Table 3 presents research questions related to use behaviors and the potential role of e-cigarettes in harm reduction and smoking cessation. The questions identify the need for appropriate standards to measure their effects in clinical studies and how to evaluate the potential opportunity that e-cigarettes represent for cessation of combustible tobacco and nicotine.

Research gaps that may be best addressed by NIH were considered. For example, clinical studies with e-cigarettes are hampered by the lack of device standards and the rapid pace of device

Table 2. Key Research Gaps: Design, Biomarkers, and Appeal

Design and constituents
• What are the characteristics of the different brands and types of e-cigarettes (constituents, dose, stability under different storage conditions, voltage and temperature, particle size and density, lung deposition, changes during use, and so on)?
• What are the most important design features that impact health, appeal (sensory aspects), and addiction potential?
• What are the most important constituents (e.g., nicotine, minor tobacco alkaloids, monoamine oxidase inhibitors, pyrazines, propylene glycol, glycerol, and so on) including flavorants and impurities in the liquids and aerosols that impact health, appeal (sensory aspects), and addiction potential?
• How do the aerosol constituents vary by device and user variables (topography, temperature and so on)? What toxicants are created in the generation of the aerosol? What is the potential for pharmaceutical interactions?
• What are the pharmacokinetics of nicotine across products? How does the nicotine pharmacokinetics differ between e-cigarettes and conventional cigarettes?
• How should toxicity be measured and what are acceptable levels of toxicity?
• What design and composition features of e-cigarettes contribute to minimizing health risks (e.g., minimal/no toxicants, stable and low temperature, minimal or high addiction potential, sealed liquids to block tampering vs. user-accessible constituents)?
Indicators of health risk, addiction, and sensory appeal
• How do people use the devices (e.g., puff duration, change in topography over time, flow rate, patterns, and frequency of use) and how does use vary by product design?
• What are the relevant pulmonary, cardiovascular, cancer, and fetal toxicity biomarkers to assess the acute and chronic effects of e-cigarettes, evaluating both the e-cigarette overall and the individual constituents? What biomarkers can predict health effects?
• What are the health effects of dual or poly-tobacco use compared with e-cigarettes alone or to conventional cigarette products? How do e-cigarettes compare with medicinal nicotine products? What quantitative measures can accurately assess extent of dual use?
• What are the health effects of secondhand and thirdhand exposure to e-cigarette aerosol?
• How should the abuse liability of e-cigarettes be measured and how do e-cigarettes compare with other tobacco and nicotine only containing products?
• How do sensory effects contribute to the abuse liability of e-cigarettes? How are these measured and what are the mechanisms of these effects (peripheral vs. central nervous system)? What role do they play in learned behavior and relapse?
• What role does nicotine in varying doses versus sensory aspects play in the e-cigarette's addiction potential (e.g., subjective effects, withdrawal suppression, concurrent tobacco use, relapse)?
• What characteristics of e-cigarettes make users of conventional cigarettes consider switching?
• Are there different characteristics of use or of the user population among different generations of e-cigarettes?
• What experimental models or self-reports could be used to predict addictiveness or toxicity?

Table 3. Key Research Gaps: Behavior, Cessation, and Harm Reduction

Behaviors of use
• How are e-cigarettes used by current, former, and never-smokers? Is conventional cigarette use affected (measured using cohort studies, analyses of pattern of use, and retail outlet geocoding)? Are the social patterns of use different between e-cigarette and conventional cigarette users?
• How can modeling and population surveillance techniques be used to estimate and understand trends in use (e-cigarette uptake, complete or partial substitution for cigarettes, and as gateway to smoking cigarettes) and factors moderating these trends?
• Do e-cigarettes delay or facilitate cessation? What characteristics influence cessation?
• How is dual use defined? What are the patterns of and reasons for dual use? Does dual use lead to conventional cigarette or nicotine cessation? Does dual use lead to altered addiction levels or changes in health risk? What factors can decrease the likelihood of sustained dual use?
• How will use of e-cigarettes affect smoking prevalence and morbidity and mortality outcomes?
• Does e-cigarette availability affect uptake by former users? Can this lead to smoking relapse?
• Does e-cigarette availability lead to uptake in never-smokers? Does this substitute or complement uptake of conventional cigarettes?
• How should relative risk information be communicated to consumers, health professionals, and adolescents? How do clinicians view e-cigarettes?
• What guidance are clinicians providing to patients on e-cigarettes? Are they providing guidance on e-liquid toxicity and unintentional exposures, especially for infants and young children?
• What are the attitudes, knowledge, and beliefs about e-cigarettes? How do they affect behavior? How do various advertisement channels and messages affect attitudes, knowledge, belief, and behavior? How do messages about e-cigarettes conveyed by family and peers affect use?
• Is it possible to encourage users of conventional cigarettes to transition to e-cigarettes, while continuing to discourage e-cigarette use among youth and former cigarette smokers?
• How do changes in product types, cost, and availability affect uptake and continued use?
Cessation and harm reduction
• What is the efficacy of e-cigarettes in cessation of conventional cigarettes or nicotine, either alone (placebo or nicotine e-cigarettes) or with approved therapies? How will e-cigarette use affect exposure biomarkers and toxicants? Will nicotine fading be an effective treatment?
• What roles do nicotine delivery and behavioral aspects of e-cigarettes have in cessation of combustible tobacco or nicotine?
• Are there acceptable outcome measures unique to e-cigarettes short of cessation, such as level of combustible use, toxicant exposure, degree of dependence?
• Who are the best candidates for cessation or conventional cigarette reduction intervention with e-cigarettes? What are the unique considerations for special populations, individuals with comorbidities, or institutionalized populations?
• What is the optimal instructional set in a clinical study for using e-cigarettes to replace conventional cigarettes or for nicotine cessation? Are there complexities unique to e-cigarettes due to the variability of nicotine puff yield between naïve and experienced users?
• How can cessation opportunities with e-cigarettes be maximized?
• What is the population reach of e-cigarettes; is it different from approved cessation products?

evolution. Many clinical studies cannot begin without an IND for a chosen e-cigarette. IND approval requires a level of product data and manufacturing documentation that is currently unavailable to many researchers. The research community needs to have access to a standard, well-characterized e-cigarette for clinical studies. Creating this resource and making it generally available for researchers is a large task that would benefit from the coordination and experience of NIH. In addition, NIH has experience in coordinating some of the large annual surveys of tobacco use and adolescent behavior. These may be considered a model for initiating more frequent studies to assess e-cigarette use in order to obtain more timely information about this rapidly moving phenomenon. Addressing e-cigarette knowledge gaps and facilitating e-cigarette research should be a priority for NIH.

Conclusions

There is extensive public discussion on whether e-cigarettes could substantially reduce conventional cigarette smoking, be an effective aid for nicotine cessation, or both. However, there is limited data available that directly addresses these issues. Concerns have also been raised about the potential for e-cigarettes to facilitate nicotine addiction, especially among youths and young adults, and to promote relapse among former smokers. The short-term and long-term effects of e-cigarettes on human physiology and behavior have yet to be fully explored. Independent, peer-reviewed research is the appropriate mechanism to evaluate e-cigarettes to assess both the potential risks and potential opportunities they represent.

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Declaration of Interests

MLG has received research funds from Pfizer. JEH, through his employer, Pinney Associates, provides consulting services to GlaxoSmithKline Consumer Healthcare regarding smoking cessation and to NJOY, a marketer of electronic nicotine delivery systems. JEH has a financial interest in a potential nicotine replacement therapy. JRH has received consulting fees from many for-profit and nonprofit developers and marketers of pharmacological and behavioral treatments for smoking cessation and organizations engaged in tobacco control. CAO is receiving free nicotine and placebo inhaler from Pfizer for an NIH-funded study of nicotine replacement for smoking cessation during pregnancy. CAO has previously received grant support from Pfizer and Nabi Biopharmaceuticals, and has also served on an advisory board for Pfizer. JER has received research funding support in the past from Philip Morris, United States, and has consulting and patent purchase agreements with Philip Morris International for nicotine inhalation technology. KMW was previously an employee in Neuroscience Discovery Research at Pfizer.

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Wound Healing and Infection in Surgery: The Pathophysiological Impact of Smoking, Smoking Cessation, and Nicotine Replacement Therapy

A Systematic Review

Lars Tue Sørensen, MD

Objective: The aim was to clarify how smoking and nicotine affects wound healing processes and to establish if smoking cessation and nicotine replacement therapy reverse the mechanisms involved.

Background: Smoking is a recognized risk factor for healing complications after surgery, but the pathophysiological mechanisms remain largely unknown.

Methods: Pathophysiological studies addressing smoking and wound healing were identified through electronic databases (PubMed, EMBASE) and by hand-search of articles' bibliography. Of the 1460 citations identified, 325 articles were retained following title and abstract reviews. In total, 177 articles were included and systematically reviewed.

Results: Smoking decreases tissue oxygenation and aerobe metabolism temporarily. The inflammatory healing response is attenuated by a reduced inflammatory cell chemotactic responsiveness, migratory function, and oxidative bactericidal mechanisms. In addition, the release of proteolytic enzymes and inhibitors is imbalanced. The proliferative response is impaired by a reduced fibroblast migration and proliferation in addition to a downregulated collagen synthesis and deposition. Smoking cessation restores tissue oxygenation and metabolism rapidly. Inflammatory cell response is reversed in part within 4 weeks, whereas the proliferative response remains impaired. Nicotine does not affect tissue microenvironment, but appears to impair inflammation and stimulate proliferation.

Conclusions: Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complications. Smoking cessation restores the tissue microenvironment rapidly and the inflammatory cellular functions within 4 weeks, but the proliferative response remain impaired. Nicotine and nicotine replacement drugs seem to attenuate inflammation and enhance proliferation but the effect appears to be marginal.

(*Ann Surg* 2012;255:1069–1079)

For a number of decades, there has been a growing amount of literature demonstrating that smoking has a negative impact on both wound healing and tissue repair. This has been demonstrated across all surgical specialties and highlights a significantly higher risk of adverse healing events after surgery including tissue flap necrosis, wound and sutured tissue dehiscence, and surgical site infections. Smoking has also been associated with longer-term complications such as fistulas, a lack of bone fusion, and incisional hernia.[1–6]

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Wound and tissue healing may be defined as the reaction of the organism to restore the continuity and function of the damaged tissue or organ. The variety of healing complications associated with smoking suggest that it may be impacting at a number of different pathophysiological levels. Smoking affects many biologic processes and is contributory to cancer, atherosclerosis, chronic obstructive pulmonary disease, and degenerative disorders. There is reason to believe that many of the molecular and cellular mechanisms associated with the healing process are affected by smoking. However, the pathophysiological impact of smoking on impaired wound healing remains unclear. Equally, there is uncertainty whether any of the important mechanisms associated with defective wound healing induced by smoking are reversible by smoking cessation.

This review aims to clarify the effect of smoking and smoking cessation on wound healing by systematically reviewing the impact and reversibility of smoking on the mechanisms involved in healing processes following surgery. In addition, the impact of nicotine and nicotine replacement therapy in abstinent smokers on healing mechanisms will be reviewed.

MATERIAL AND METHODS

A formal computerized search in the databases MEDLINE (1963–2010) and EMBASE (1985–2010) was performed to identify relevant studies according to the search strategies listed in Table 1 and Figure 1. In addition, a manual cross-reference search of all potentially eligible papers retrieved for full-text evaluation was undertaken. From the electronic search 1460 citations were identified. After title and abstract review, 325 articles were retained as eligible. A full-text evaluation resulted in 177 studies to be included for systematic review (Fig. 1).

RESULTS

The Impact of Smoking on Wound Hemostasis and Inflammation

Immediately after wounding, the coagulation cascade and platelets are activated to form a thrombus in the wound cavity. The formation of this hemostatic clot, the composition of which is predominantly polymerized fibrin cross-linked with fibronectin,[7] is enhanced by smoking as a result of platelet activation and blood fibrinogen release.[8–10] In smokers' blood and probably also in the wound clot, there is a higher concentration of fibronectin, probably due to the effect of oxidative injury on vascular endothelial cells.[11,12] The clot composition with respect to cytokines, chemoattractants, and growth factors appears to be altered by smoking. For example, there is a reduction in platelet-derived growth factor and transforming growth factor-β1 (TGF-β1) suggestive of a decrease in inflammatory stimulatory wound components.[13]

Shortly after hemostasis, the inflammatory phase of healing is initiated as inflammatory cells and fibroblasts migrate into the wound from capillaries in the wound periphery using the matrix components

Non Specific Pain Diagnoses

Question: Where should non-specific pain diagnoses be prioritized and what treatments should be allowed for these types of conditions?

Question source: HSD, HERC staff

Issue: There are several ICD-10 codes in the G98 series that are currently not on the Prioritized List and therefore not available for pairing with any treatment.

From an outside provider:

> EOCCO is not accepting this code [G89.29] as a primary diagnosis and the MMIS indicates that "a more definitive diagnosis is required". We would like the State to reconsider their decision on this code and accept it as a primary diagnosis. As you can see from the attached coding guidelines, depending upon the reason for the encounter, it is appropriate that this code be submitted as a primary diagnosis with the underlying cause of the pain reported as an additional diagnosis. We feel that proper coding guidelines support the coding for our claim.

Currently, G89.4 (Chronic pain syndrome) is on line 533 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS.

Current Code Placement

ICD-10 code	**Code description**	**Current placement**
G89.11	Acute pain due to trauma	Diagnostic Workup File (DWF)
G89.21	Chronic pain due to trauma	Undefined Diagnosis File
G89.28	Other chronic postprocedural pain	Undefined Diagnosis File
G89.29	Other chronic pain	Undefined Diagnosis File

HERC staff recommendations:

Step 1: Prioritize vague chronic pain to an uncovered line consistent with current diagnoses prioritization

1) Leave ICD-10 G89.11 (Acute pain due to trauma) on the DWF
    a. Allow for xrays, labs, other testing to determine cause of pain
2) Add ICD-10 G89.21 (Chronic pain due to trauma), G89.28 (Other chronic postprocedural pain) and G89.29 (Other chronic pain) to line 533 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS
3) Advise HSD to remove ICD-10 G89.21, G89.28 and G89.29 from the Undefined Diagnosis File

Step 2: Discuss creation of a new line for chronic pain with limited treatments for the 2020 Biennial Review

1) Issues to consider:
    a. What other diagnoses to include (fibromyalgia? Complex regional pain syndrome?)
    a. What treatments to include (CBT, acupuncture, PT?)
    b. Line scoring
2) Possible creation of a taskforce

MRI for MS Monitoring

Question: Should MRI be covered for monitoring asymptomatic patients for MS progression? If not, should the current MRI in MS guideline be modified to allow some use of MRI in certain clinical situations?

Question source: Laura Schaben, MD; Michael L. Bell, MD; various other neurologists in Oregon

Issue: MRIs are frequently used by neurologists to diagnose MS and to evaluate the effect of disease modifying therapy. Many neurologists recommend yearly MRIs of all MS patients to monitor therapy and to decide to modify therapy if new plaques or other changes are detected.

The use of MRI for monitoring asymptomatic MS patients was reviewed in August, 2013. At that time, NICE and the European Federation of Neurological Societies Summary of Guidelines were reviewed, and did not recommend routine MRI for monitoring stable patients. Based on the lack of evidence that monitoring asymptomatic patients would change management or outcomes, the HERC adopted a new diagnostic guideline which limited MRI to diagnosis of MS, but prohibited use for routine monitoring of disease.

Since that MRI in MS guideline has gone into effect, there has been considerable feedback to the Medical Directors and HERC staff from community neurologists expressing disagreement with this guideline. Specifically, neurologists generally consider regular (yearly or more frequent) MRI to be necessary to monitor medication effectiveness and identify new MS activity in the brain before clinical symptoms arise, in order to better modify medications. Since the new MRI in MS guideline has gone into effect, there has been multiple complaints to the various CCOs. The CCO medical directors indicate that they are reviewing requests for MRIs and approving those that seem appropriate. Generally, these MRIs are for evaluation of patients with new objective symptoms, or for monitoring for safety in certain clinical situations in which patients are at higher risk of complications from medications.

CCOs are reporting that neurologists are discharging OHP MS patients from their care because they cannot monitor their disease with yearly MRIs and therefore they cannot provide standard of care. These neurologists point to specialty guidelines which recommend regular MRIs for both asymptomatic patients and in various clinical scenarios.

Current Prioritized List Status

MRI CPT codes are on the Diagnostic Fist

- 70551 MRI, brain without contrast
- 72141 MRI, cervical spine without contrast
- 72146 MRI, thoracic spine without contrast
- 72148 MRI, lumbar spine without contrast

DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease

MRI for MS Monitoring

Evidence

1) **MED 2016**, MRI for monitoring progression of MS
    a. Staff did not find any systematic reviews (SRs) or meta-analyses (MAs) assessing the impact of MRI on mortality
    b. There are no SRs or MAs demonstrating that MRI monitoring for MS progression changes clinical management or outcomes.
    c. Conclusions: The Center search revealed no studies to support that MRI contributes to improved disease outcomes in MS
    d. Clinical practice guidelines
        i. Two recent poor-quality clinical practice guidelines recommend the use of MRI monitoring at least yearly in patients with MS treated with disease modifying therapy (DMTs). More frequent monitoring is recommended for patients treated with natalizumab who are risk of developing progressive multifocal leukoencephalopathy (PML)
2) **NICE 2014**, management of MS in adults https://www.nice.org.uk/guidance/cg186/resources/multiple-sclerosis-in-adults-management-35109816059077
    a. Made no comments about the use of MRI other than for diagnosis of MS

Expert group recommendations:

1) **Magnetic Resonance Imaging in MS (MAGNIMS) 2015**, guidelines for MRI monitoring in MS
    a. Regular brain MRI scans are essential for monitoring disease progression in patients with MS
    b. Follow-up scans should be conducted at least annually, and as often as every 3–4 months in patients who require enhanced pharmacovigilance
        i. Patients who require enhanced pharmacovigilance include patients treated with natalizumab who are JCV seropositive
        ii. patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate)
            1. scans every 3-4 months for 12 months
2) **Consortium of MS Centers Task Force 2015**, recommendations for MRI in MS
    a. Timing of brain MRI protocol with gadolinium for patients with an established diagnosis of MS
        i. No recent prior imaging available (eg, patient with MS transferring to a new clinic)
        ii. Postpartum to establish a new baseline
        iii. Prior to starting or switching disease-modifying therapy
        iv. Approximately 6 months after switching disease-modifying therapy to establish a new baseline on the new therapy
        v. Every 1–2 years while on disease-modifying therapy to assess subclinical disease activity
        vi. Unexpected clinical deterioration or reassessment of original diagnosis
        vii. Timing of PML surveillance brain MRI protocol
        viii. Every 12 months for patients negative for serum JC virus antibody
        ix. Every 3–6 months for patients positive for serum JC virus antibody and ≥18 months on natalizumabb

MRI for MS Monitoring

Expert input:

Full testimony from Dr. Michael Bell and Dr. Laura Schaben are included in the packet.

Excerpt from testimony from Dr. Michael Bell:

> MRI is an invaluable tool in following MS disease activity. This relates to the fact that 4 out of 5 new MS plaques are clinically silent (that is only apparent on MRI imaging since the new attack causes no acute symptoms). Thus, the new attitude as expressed to me by Alison Little yesterday, "why don't you just follow the disease clinically" results in 80% of an MS patients new lesions going unrecognized. Despite the lack of acute symptoms from clinically silent lesions, the accumulation of these lesions over time does cause progressive disability, such as cognitive impairments, coordination/gait impairments, urinary incontinence, weakness, and spasticity. Multiple long term studies of disease modifying therapies have robustly shown that early intervention slows the rate of progression of disability. The standard of care in MS is to follow patients with MR imaging to see if the disease modifying therapy they take is successful, given the multiple different mechanism drugs now available for MS. If a particular drug proves unsuccessful radiographically, we modify therapy to find an effective drug.

Dr. Schaben feels that the proposed guideline is acceptable. Dr. Bell indicates that yearly MRI for monitoring of response to therapy should be covered.

HERC staff summary:

Expert guidelines recommend regular MRI monitoring of patients with MS, particularly those who require higher pharmacovigilance. However, there is no evidence that routine MRI monitoring of asymptomatic MS patients affects disease progression or outcomes.

Neurologists feel very strongly about the inappropriateness of the current HERC guideline. Pragmatic changes could be made to the guideline to address the issues of greatest concern to this provider group; however, such changes would be based upon expert opinion. These changes are acceptable to the CCO medical directors.

MRI for MS Monitoring

HERC staff recommendation:

1) Modify Diagnostic Guideline D10 as shown below

DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

MRI may be considered in the following circumstances:

1) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes
2) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected
3) Patients who require enhanced pharmacovigilance, including
    a. Yearly monitoring for patients treated with natalizumab who are JCV seropositive
    b. One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab

Written testimony from Dr. Michael Bell

I understand that you are the medical director of the Health Evidence Review Commission, involved in the recent decision to put MRI use in multiple sclerosis "below the line" of coverage for OHP patients. As a general neurologist practicing in Bend, Oregon, I would like to express my dismay at this decision, which has hamstrung my ability to appropriately manage patients with this devastating disease. I have copied this email to my partner, Laura Schaben MD, who is a multiple sclerosis specialist. She has had conversations with multiple MS specialists across the state who all share my dismay.

As you know, multiple sclerosis is a chronic inflammatory disease damaging the central nervous system. In the past decade, treatments for multiple sclerosis have advanced tremendously with multiple new disease modifying therapy options, some proven significantly more powerful than the previously existing interferon therapies and copaxone.

MRI is an invaluable tool in following MS disease activity. This relates to the fact that 4 out of 5 new MS plaques are clinically silent (that is only apparent on MRI imaging since the new attack causes no acute symptoms). Thus, the new attitude as expressed to me by Alison Little yesterday, "why don't you just follow the disease clinically" results in 80% of an MS patients new lesions going unrecognized. Despite the lack of acute symptoms from clinically silent lesions, the accumulation of these lesions over time does cause progressive disability, such as cognitive impairments, coordination/gait impairments, urinary incontinence, weakness, and spasticity. Multiple long term studies of disease modifying therapies have robustly shown that early intervention slows the rate of progression of disability. The standard of care in MS is to follow patients with MR imaging to see if the disease modifying therapy they take is successful, given the multiple different mechanism drugs now available for MS. If a particular drug proves unsuccessful radiographically, we modify therapy to find an effective drug. This is exactly analogous to CT imaging for a cancer, upgrading chemo if the cancer is failing to respond to therapy. Dr. Little's suggestion to me yesterday to just use my clinical judgment would result in lost opportunities, increased plaque burden, and more rapidly developing disability. Furthermore, when plaques accumulate over time, axonal degeneration ensues resulting in the untreatable phase of MS, "secondary progression." In other words, these plaques, most initially clinically silent, are not benign over time but result in a progressive and untreatable second phase of MS.

Imagine telling oncologists to follow cancer without CT imaging! Obviously, the result would be lost opportunities to control the cancer at earlier phases. MS is precisely analogous.

Furthermore, the result of this policy has been that when patients need an MRI scan for MS, I am forced to send them to the emergency room for much more expensive care. Yesterday, I had a patient with MS who had a possible new attack. I thought the lesion could however be a pseudoattack, or old plaque causing recurrent symptoms. MRI would easily sort this out, but since it is not covered I had to send her to the ER where an MRI was done. Shifting care of this chronic outpatient disease to the emergency room is not a step towards cost effective care.

Dr. Little did notify me that the Health Evidence Review Commission would require studies

showing that MRI imaging in MS improves outcomes. Such a study will never be done, because it is so evident that MRI is an invaluable tool in MS. Asking for such a study is analogous to asking skydivers to do a placebo controlled trial to determine if parachutes prevent gravitational injury in individuals who jump out of airplanes. (see **Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials** BMJ 2003;327:1459) Maybe a better analogy would be flying an airplane blindfolded without instruments. We have a tool to visualize MS plaques, which cause the disability in MS. With powerful drugs to control the progression, why would you deny us the use of this tool?

Before I approach my local newspaper to cover a story on this shameful neglect of our MS population in Oregon, I would like the give the state the opportunity to rethink this decision. If there are any other individuals involved in this decision that I could continue this discussion with, please let me know. I would welcome a phone call if you would like to discuss these matters further.

Michael L. Bell, MD
General Neurologist, Bend Neurological Associates
Bend Oregon

Later response:
Thank you for your attention to this issue. We greatly appreciate that you are allowing us to have some limited use this very valuable tool in assessing MS as below. The other huge role of MRI in MS patients is assessing drug effectiveness, since 9 of 10 MS attacks are clinically silent so if we only scan when patients have symptoms with objective exam findings we will often be delayed in recognizing active disease/treatment failure. Although silent MS attacks do not cause symptoms acutely, the chronic accumulation of these plaques do cause the long term disabilities due to MS such as cognitive impairments, gait impairments, spasticity, urinary incontinence, and fatigue. There are two situations that the guidelines below do not address. The first is monitoring drug success. Generally, an MRI when a new drug is initiated followed by another scan periodically (initially every year or two, less frequently over time if a drug is working well) can assess drug success to enable us to step up to more effective therapies if MS plaques are continuing to accumulate. Given the new more powerful MS treatments available, generally with more significant side effects, this step wise approach to the treatment of MS has been advocated by MS thought leaders such as Brian Weinshenker at Mayo Clinic (which was the subject of the April 2016 American Academy of Neurology Plenary Session by Dr. Weinshenker who argued that starting with milder drugs, with careful surveillance (clinical and MRI) to step up therapy over time for treatment failure is the safest approach to MS treatment). The second role of MRI not well addressed with the guidelines below is when patients present with focal symptoms and physicians are not sure if these are new attacks or pseudoattacks. MRI is the tool to distinguish this. The patient's exam often does not show clear-cut new exam findings in this situation, even if a real MS attack. Thus in guideline 1 below I would love to see the requirement for objective changes in neurological status removed and instead leave it as "suspected drug failure / new clinical

symptoms." Guideline 2 I'd prefer to see "evaluation of progression with new clinical symptoms" with the term objective removed to clarify that exam findings are often not present for example in a patient with worsening urinary urgency or limb numbness. I certainly do understand that many neurologists have relied on excessively frequent MRIs in the surveillance of inactive disease, and feel that in asymptomatic patients some sort of limitation to the frequency of MRI for disease surveillance would be very reasonable to reign in costs. I've observed neurologists scan patients every 6 months or even every 3 months to follow drug effectiveness in asymptomatic patients, and feel limiting surveillance to every 1-2 years would be a powerful way to reign in costs.

I hope this is helpful, and please feel free to share this as written testimony for the meeting. I would love to join you by phone to testify as well on March 9th.

Michael Bell, MD

Written testimony from Dr. Laura Schaben

I am in complete agreement with Dr. Bell that this policy is harmful to patients and creates a 'two tier' system where patients on OHP receive a different and inferior level of MS care because of lack of access to MRI imaging. I follow the Consortium of MS Centers guidelines on MRI imaging in MS which is referenced below. Please note this is a consensus document representing the opinion of top experts in the field of MS in the United States and Canada. The issue of how to best use MRI in MS is complicated given the tremendous variability from patient to patient with MS- some patients need scans as seldom as every 5 or 10 years and others with very aggressive and treatment refractory disease may need imaging every 2-3 months, as a series of medications is tried. Its also important to stress that MS is the leading cause of non-traumatic neurological disability in young adults, and if not adequately treated, leads to a lifetime of serious neurological disability (cognitive and physical). With expert treatment much of this disability can be avoided.

While MRI is essential in the diagnosis of MS, it is also critical in evaluating response to treatment, and in the safety monitoring of patients on MS medications that have risk of JCV infection (PML). PML (progressive multifocal leukoencephalopathy) is a life threatening disease that can occur as a complication of Tysabri, Gilenya and Tecfidera treatments. If undetected it is often fatal, while if detected early treatment is usually effective. It is recommended currently that annual MRI brain be performed in all patients on Tysabri because PML risk. Lack of appropriate safety monitoring certainly could be considered medical malpractice.

I hope you terminate this harmful policy. I have already seen patients harmed by this policy and have resorted to sending patients to the emergency room now when a scan is needed which is costly and inconvenient. The bottom line is that periodic MRI is needed in patients with an established MS diagnosis, and that this policy is harming patients.

Updated MS Consortium Guidelines can be found at these links:
http://www.ajnr.org/content/early/2015/11/12/ajnr.A4539.abstract
http://c.ymcdn.com/sites/www.mscare.org/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECEE07B/MRIProtocol2015_updated102015.pdf

Thank you for your consideration of this serious matter.

Later response:
[The proposed guideline] looks good to me the way you have written it. I would comment that the listed MRI studies in the attached document are "without contrast" and MRI "with and without contrast" is the type of study needed to evaluate for acute MS related inflammation (as the actively inflamed lesions are contrast positive). I also note the document states one neurology clinic is concerned (meaning Dr. Bell and myself) but I would just point out that I have have been contacted by and discussed this issue with concerned neurologists outside of our group as well (specifically Dr. Ferenz who was formerly at BMC neurology, and another neurologist from the Dalles area that I can track back down if it's relevant).

EVIDENCE-BASED GUIDELINES

MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients

Mike P. Wattjes, Àlex Rovira, David Miller, Tarek A. Yousry, Maria P. Sormani, Nicola de Stefano, Mar Tintoré, Cristina Auger, Carmen Tur, Massimo Filippi, Maria A. Rocca, Franz Fazekas, Ludwig Kappos, Chris Polman, Frederik Barkhof and Xavier Montalban on behalf of the MAGNIMS study group

Abstract | The role of MRI in the assessment of multiple sclerosis (MS) goes far beyond the diagnostic process. MRI techniques can be used as regular monitoring to help stage patients with MS and measure disease progression. MRI can also be used to measure lesion burden, thus providing useful information for the prediction of long-term disability. With the introduction of a new generation of immunomodulatory and/or immunosuppressive drugs for the treatment of MS, MRI also makes an important contribution to the monitoring of treatment, and can be used to determine baseline tissue damage and detect subsequent repair. This use of MRI can help predict treatment response and assess the efficacy and safety of new therapies. In the second part of the MAGNIMS (Magnetic Resonance Imaging in MS) network's guidelines on the use of MRI in MS, we focus on the implementation of this technique in prognostic and monitoring tasks. We present recommendations on how and when to use MRI for disease monitoring, and discuss some promising MRI approaches that may be introduced into clinical practice in the near future.

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Introduction

The valuable contribution of MRI to the diagnosis, and particularly the differential diagnosis, of multiple sclerosis (MS) has been highlighted in many review articles and position papers.[1–3] Additionally, the use of MRI for MS diagnosis has accelerated since the introduction and subsequent revisions of the International Panel criteria for the diagnosis of MS (also called the McDonald criteria).[4–6] Nonetheless, the use of MRI in follow-up monitoring of MS disease activity has been somewhat overlooked, despite the fact that this technique offers promising prospects for patient care.

The potential for MRI measures to facilitate the assessment and monitoring of treatment efficacy is well recognized. With the approval of a new generation of MS drugs, the applications of MRI in treatment monitoring have broadened beyond tracking of disease progression to include detection of opportunistic infections and paradoxical reactions. The emerging pharmacological approaches that target pathogenetic pathways for preventing MS progression (for example, by promoting remyelination) will require new imaging approaches to monitor disease activity.[7–9]

In the second part of the MAGNIMS consensus guidelines on the use of MRI in patients with MS, we focus on prognostic and monitoring applications. This report provides recommendations from an expert panel on how and when to use MRI for disease and treatment monitoring, how to establish prognosis, and how to assess the efficacy and safety of treatments. In addition, we discuss new, promising MRI techniques that might become clinically relevant in the near future.

Competing interests
The authors declare no competing interests.

Methods

In June 2011, an international panel convened in Barcelona, Spain to discuss the use of MRI in patients with MS. This meeting was held under the auspices of MAGNIMS, an intellectually independent network of European clinical research groups that have an interest in the use of MRI to study patients with MS. The panel was composed of experts in the diagnosis and management of MS, and included neuroradiologists, neurologists and statisticians from nine MAGNIMS-affiliated institutions across six different countries (Box 1). The panel met to present and discuss data from research published in English, and to consider the recommendations contained in previous papers related to the use of MRI in patients with MS.

After the meeting, the panel set out to create specific and up-to-date recommendations for the implementation (planning, performance and interpretation) of brain and spinal cord MRI in the diagnostic process for patients with suspected MS.[10] For this companion piece, the panel has established a similar set of recommendations on the use of MRI to monitor MS disease activity and establish disease

Box 1 | The MAGNIMS network

The authors are members of the MAGNIMS (Magnetic Resonance Imaging in MS; http://www.magnims.eu/) network, a group of European clinicians and scientists with an interest in collaborative studies using MRI methods in patients with multiple sclerosis. The network is independent of any other organization and is run by a steering committee whose members are:

- Nicola de Stefano (co-chair), Department of Neurological and Behavioural Sciences, University of Siena, Italy
- Àlex Rovira (co-chair), Magnetic Resonance Unit, Hospital Vall d'Hebron, Barcelona, Spain
- Frederik Barkhof, Department of Neuroradiology, VU University Medical Centre, Amsterdam, Netherlands
- Olga Ciccarelli, Institute of Neurology, Queen Square, University College London, UK
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prognosis. During the 3 years after the meeting in Spain, the panel analysed relevant publications on the application of brain and spinal cord MRI for prognostication and for monitoring of disease activity and treatment efficacy. These guidelines were first drafted by the principal author, and were based on contributions from each panellist, assigned according to their area of expertise. The first draft was then circulated to all members, who iteratively modified the document until a consensus agreement was reached on the final guidelines.

Prognostic value of baseline MRI

Conventional MRI measures, such as T2 lesion load, do not fully correlate with clinical measures of disability in patients with MS,[11] but there is increasing evidence that certain imaging data obtained early in the disease course can serve as prognostic markers for disability accumulation at early and late follow-up.[12] A large 20-year follow-up study showed that the MRI T2 lesion load in patients with clinically isolated syndrome (CIS) was associated with the conversion rate to definite MS.[13] In the same study, 79% of patients with CIS who had normal brain MRI findings at baseline did not convert to definite MS after 20 years of follow-up. A similar association was found in a large optic neuritis trial, demonstrating that high baseline lesion number is associated with an increased risk of converting to definite MS.[14]

The number of T2 lesions in patients with CIS has also been associated with disability accumulation, as measured by the Expanded Disability Status Scale (EDSS).[13] However, subsequent research indicated that the topography of the lesions, in addition to the total number, has prognostic value in patients with CIS. Infratentorial lesions are of particular importance: the presence of at least one cerebellar lesion is related to an elevated conversion rate to definite MS, and the presence of at least one brainstem lesion is also associated with a higher risk of conversion, as well as increased disability accumulation.[15] The relevance of infratentorial lesions in relation to clinical outcome was further underscored in a study showing that spinal cord lesions, infratentorial lesions and contrast-enhancing lesions in patients with optic neuritis have predictive value for disability accumulation at 6-year follow-up.[16] Furthermore, the presence of at least two infratentorial lesions in patients presenting with CIS seems to have high predictive value for long-term disability.[17]

MRI monitoring of disease course

Several guidelines have tried to define the indications for and frequency of serial MRI in adults and children with an established diagnosis of MS.[18–20] In general, the recommendation is that patients should be further evaluated with MRI after each unexpected clinical presentation that might be related to MS (such as unexplained or atypical symptoms of disease activity), or is not typical of MS (for example, suspected comorbidity such as vascular or neoplastic disease, or adverse effects of treatments). Treated patients with MS are a heterogeneous population with different levels of disease activity and susceptibility to drug-related adverse events. Follow-up MRI can reveal multiple measures of MS pathology, but the usefulness and reliability of these measures vary.

Focal lesions

Brain MRI is very sensitive for monitoring of disease activity and treatment efficacy in patients with MS, and parameters related to image acquisition (for example, pulse sequences, spatial resolution and MRI hardware) are relatively easy to standardize, particularly in a single-centre setting. MRI of the spinal cord is less sensitive than brain MRI for detecting disease activity, particularly with regard to contrast-enhancing lesions.[21,22] This limitation arises from the technical challenges of spinal cord MRI acquisition—relating mostly to image artefacts associated with vascular and cerebrospinal fluid pulsation—and the difficulty of standardizing the assessment of lesion count and lesion volume. In addition, most spinal cord lesions are clinically symptomatic, and a strong relationship exists between the development of new lesions in the brain and the development of new lesions in the spinal cord.[23] Taken together, these issues indicate that serial spinal cord imaging for the detection of new focal lesions might add little to brain imaging for monitoring of disease activity and progression. Thus, the relevance of spinal cord imaging for routine follow-up seems rather limited.

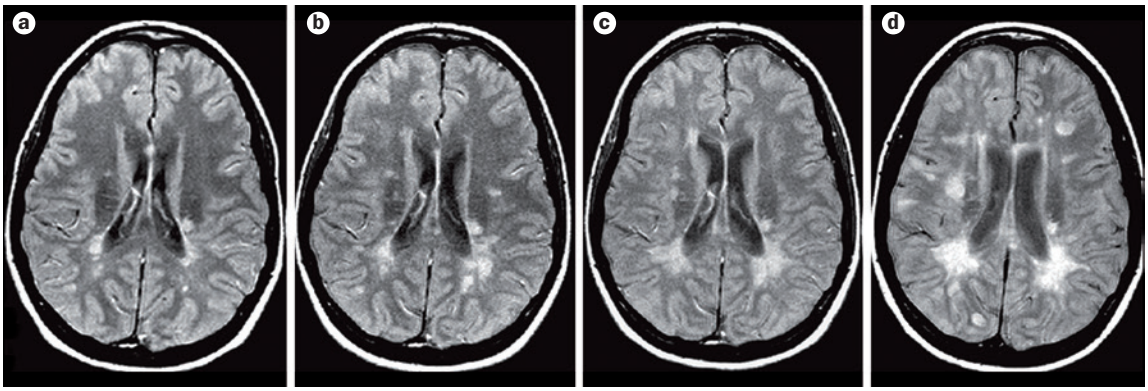

Figure 1 | Serial MRI in a patient with relapsing–remitting multiple sclerosis. Proton-density weighted MRI scans obtained at **a** | baseline, and **b** | 1 year, **c** | 2 years and **d** | 3 years later. Disease progression can clearly be seen in the form of new and enlarging focal lesions over time, shown here as hyperintensities (white spots).

Ideally, brain MRI should be performed on the same MRI system and using the same imaging protocol—that is, the same pulse sequences and spatial resolution—as the reference (baseline) scan. Contrast-enhanced T1-weighted sequences are recommended to detect acute inflammation. However, depending on the clinical situation and the scan interval, demonstration of active (new or enlarging) T2 lesions can deliver sufficient information about subclinical disease activity and disease progression (Figure 1).[24,25] In addition to contrast-enhancing and active T2 lesions to measure acute MS-related inflammation, several MRI markers of focal neurodegeneration should be considered, such as chronic T1 hypointense lesions ('black holes') that persist longer than 6 months.[26–29] This imaging finding may hold promise for predicting disability progression and monitoring remyelination, and represents a possible new outcome marker for MS therapies.[30,31]

Global brain volume changes

The pathological hallmark of MS is the presence of multiple focal demyelinating lesions in the cerebral white and grey matter, but substantial brain atrophy can also occur.[32] Over the past few years, several studies have used MRI-derived methods to assess brain volume changes, revealing that atrophy can be present even in the early stages of MS, and that it advances over the disease course (Figure 2).[33,34] Generally speaking, brain volume changes can be an important measure of tissue damage in patients with MS.[32] Indeed, baseline atrophy and high rates of subsequent volume loss are associated with cognitive impairment, fatigue and disability progression over the long term.[32,35–41]

In a complex disease such as MS, brain volume loss results from the sum of and interactions between various destructive pathological processes,[42] including irreversible demyelination, and axonal and/or neuronal loss. The neurodegenerative pathology that occurs in MS is an important target for treatment; thus, MRI brain volume measures have been used in randomized clinical trials to monitor the effects of disease-modifying therapies on these parameters.[26,32] In a recent meta-analysis of clinical trials, the overall effect of treatments on brain atrophy correlated with the effect on disability.[43] In many trials, however, disease-modifying drugs (DMDs) have produced only moderate evidence of a reduction in brain volume loss. Indeed, anti-inflammatory drugs have been shown to excessively decrease brain volume within the first 6 months to 1 year of treatment, followed by stabilization during the second year of treatment.[41] This phenomenon is called pseudoatrophy, and it seems to be directly associated with the resolution of ongoing white matter inflammation induced at the time of treatment initiation.[32,44–47] To identify pseudoatrophy during a clinical trial, brain volume should be measured every 3–6 months.[25]

In addition to disease-specific changes, lifestyle-related factors (including alcohol consumption, smoking, dehydration and BMI), genetics (such as the presence of an *APOE*ε4* allele), and concomitant pathophysiological conditions (such as diabetes and/or other cardiovascular risk factors) can affect brain volume. Clinical interpretation of brain volume loss in patients with MS can be difficult in the context of these other factors.[48] Moreover, differences in the quality and capabilities of MRI hardware, and in the software packages used for analysis or processing, can generate notable variability in brain atrophy assessments.[32,49]

For the above reasons, caution must be exercised when interpreting apparent changes in the rate of brain volume loss. We believe that the use of longitudinal brain volume assessment as a marker of disease progression in individual patients cannot be considered to be reliable at present. Further studies are needed to establish normative values for brain volume changes—both in healthy individuals and in patients with MS—that take the various potential confounding factors into account.

The role of advanced and quantitative MRI

Quantitative MRI techniques, including magnetization transfer[50] and diffusion tensor imaging (DTI),[51] can measure the extent of structural changes that occur within and outside focal lesions in white and grey matter. Moreover, these techniques can characterize the pathological nature of these changes, as has been shown by correlative histopathological–MRI studies.

The magnetization transfer ratio provides a quantitative estimate of the capacity of protons that are bound to the brain tissue matrix to exchange magnetization with

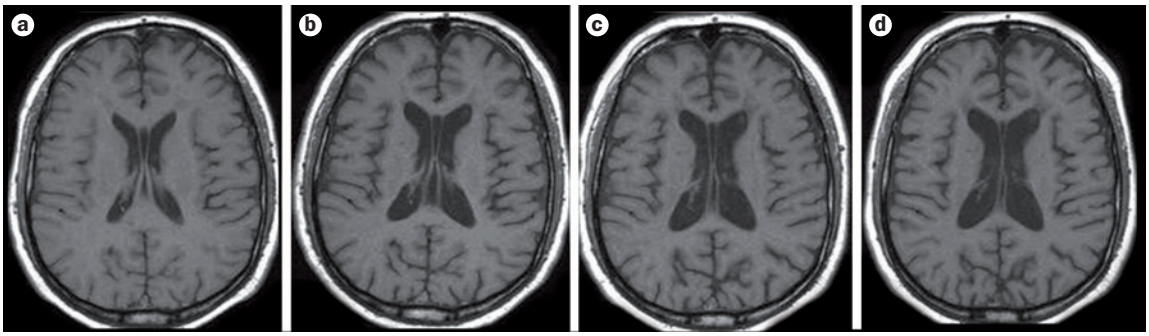

Figure 2 | Serial T1-weighted MRI scans in a patient with multiple sclerosis. **a** | Baseline scan. **b**–**d** | Regular scans over a 6-year follow-up period. Disease progression can be seen in the form of the increasing size of ventricular and subarachnoid spaces. These changes reflect brain volume loss over time, indicating progressive neurodegeneration.

the surrounding free water. Decreases in the magnetization transfer ratio have been shown to correlate with the degree of myelin loss and axonal damage in patients with MS.[52,53]

DTI is sensitive to the orientation and density of cellular structures that hinder water diffusion. The local tissue microstructure is evaluated with several indices, including mean diffusivity and fractional anisotropy, which correlate with myelin content, tissue integrity and axonal loss.[54] Proton magnetic resonance spectroscopy (^{1}H-MRS) can add information on the biochemical nature of MS-related abnormalities, by quantifying several CNS metabolites.[55] T2 hypointense areas and reduced T2* relaxation time (or its reciprocal R2*) are thought to be associated with iron deposition, which is believed to be a sign of neurodegeneration in patients with MS.[56]

Application of these techniques to characterize the extent and distribution of MS-related damage within focal lesions or in normal-appearing white and grey matter has shown that tissue disruption in patients with progressive disease is more severe and more widely distributed than in patients with relapsing forms of MS.[57] Additionally, structural CNS damage has been shown to progress at different rates across the major clinical phenotypes of MS. Global and regional quantitative MRI abnormalities correlate with the severity of clinical and cognitive impairment, and advanced and quantitative MRI techniques seem to be useful for predicting subsequent accumulation of clinical disability and cognitive impairment.[57,58]

Quantitative MRI techniques might enable measurement and monitoring of disease-related mechanisms that occur before the development of atrophy, which primarily occurs in the late stages of MS. To date, very few clinical trials have included these metrics as outcome measures.[59–62] One method that was developed to monitor changes in the magnetization transfer ratio in individual lesion voxels revealed evidence consistent with demyelination and remyelination within the same lesion. Of note, signs of remyelination were still present in some lesions 3 years after their formation.[63] The potential of quantitative MRI methods was demonstrated in a single-centre clinical trial that used magnetization transfer MRI, which suggested that alemtuzumab protects against grey matter damage.[64] A recent combined magnetization transfer MRI and ^{1}H-MRS study showed that patients treated with laquinimod tend to accumulate less microscopic white and grey matter damage than those receiving placebo.[65]

Despite these promising results, the actual contribution of advanced MRI techniques to clinical management has not been fully validated, especially in a longitudinal manner. Furthermore, their use for monitoring treatment effects is hampered by a lack of standardization between centres.[58]

Statements and recommendations

- T2-weighted and contrast-enhanced T1-weighted brain MRI are the modalities of choice for MS disease monitoring, revealing acute and active inflammation, and clinically silent disease progression[24,25]
- The use of spinal cord MRI in addition to brain MRI is not recommended for routine monitoring (in contrast to MS diagnosis), and should be limited to certain clinical situations (such as unexplained and/or unexpected spinal cord symptoms)[21–23]
- Assessment of brain volume does not have a role in the diagnostic process of MS, but can be a good predictor of long-term disability[32]
- Measures of brain volume can be used in clinical studies and as end points in clinical trials, but confounding factors and pseudoatrophy should be taken into account[44–47]
- Rates of change in brain volume are not recommended as a marker of disease progression in individual patients, owing to the technical, biological and pharmacological factors that can influence the measurement and interpretation of atrophy rate[48]
- The use of advanced MRI methods for MS disease monitoring is promising but has not been well investigated; their value is potentially limited by a lack of standardization, and advanced MRI is, therefore, not recommended for routine clinical use[57]

Evaluating response to treatment

Patients with MS who continue to experience clinical and/or MRI-visible disease activity despite treatment with DMDs are categorized as 'nonresponders'.[66–69] Early identification of nonresponders to first-line therapies would enable a prompt switch to a more effective treatment,[70] but predicting which individual patients will respond to DMDs, and to what degree, is challenging.

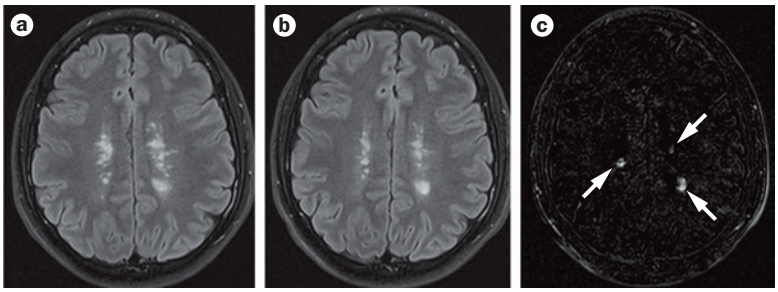

Figure 3 | Subtraction MRI in a patient with relapsing–remitting multiple sclerosis. T2 fluid-attenuated inversion recovery (FLAIR) images **a** | at baseline and **b** | after 1 year. **c** | A subtraction of these two images highlights the new and enlarging lesions (arrows).

Early prediction

Some evidence suggests that certain baseline demographic variables (for example, age at treatment initiation), clinical factors (including disease duration at treatment initiation and pretreatment relapse rate) and MRI measures related to disease activity (such as baseline lesion load) can help to indicate which patients will benefit most from a first-line DMD, and who will have a poor response.[66,71–74] However, the relevant studies mainly analysed cohorts receiving different IFN-β formulations, produced preliminary or inconsistent results, and have failed to satisfactorily predict treatment response in clinical practice.[70] Other MRI-derived metrics—such as global or regional brain volume, or the number of spinal cord lesions—have shown value for predicting relapses or disability progression,[35–37,39,75–77] but have not been specifically analysed for treatment response predictions. Therefore, the use of these measures at baseline and over follow-up is still not recommended for predicting treatment response in clinical practice.

Another approach to the prediction of treatment response is to analyse variables measured after the start of treatment, but before the actual clinical end point of interest. Several studies have attempted to define criteria and strategies for the early identification of suboptimal response in individual patients via a combination of clinical and MRI measures during the first 6–12 months after treatment initiation.[67,78–82] These criteria are partially or completely based on the detection of disease activity in follow-up brain MRI scans, defined as new gadolinium-enhancing lesions or new and/or enlarging T2 lesions compared with baseline scans.

These two measures have relevant differences. Contrast-enhancing lesions are considered to be a marker of blood–brain barrier disruption, which has been associated with inflammation in patients with MS. New T2 lesions simply reflect the permanent footprint from a previous focal inflammatory lesion that developed in the interval between two scans. Thus, we should consider two important factors when interpreting the finding of new T2 lesions: the time point when the reference (pretreatment) scan was performed, and the mechanism of action of the drug being evaluated. In clinical practice, baseline scans are commonly obtained before treatment initiation, but the time gap between baseline and follow-up might not be taken into consideration. Furthermore, some drugs, such as glatiramer acetate, require up to 6 months to become effective.[81,83] Therefore, the presence of new T2 lesions on a 6–12-month follow-up scan does not necessarily reflect suboptimal response; it could simply be ongoing disease activity during the period before treatment was initiated or before the drug became effective.[84,85] Accordingly, some experts have proposed that the reference scan should be performed 6 months after—rather than before—treatment initiation.[81,86]

Follow-up measurement

Gadolinium-enhancing lesions are typically easier to identify than new and/or enlarged T2 lesions, and the process is also less dependent on technical factors such as scan repositioning. Furthermore, some new T2 lesions can only be visually detected after being identified as new gadolinium-enhancing lesions, owing to their small size or their location in areas with confluent lesions.[87] Nonetheless, recognition of disease activity cannot rely exclusively on gadolinium-enhancing lesions. New inflammatory lesions take up gadolinium for only around 3 weeks after development,[88] and the recommended interval between baseline and follow-up scans is typically 3–6 months. Therefore, contrast-enhancing lesions are not sufficiently sensitive to act as sole measures of disease activity.

Detection of active T2 lesions can be hindered by multiple factors, including a high load of inactive T2 lesions, inadequate repositioning of serial scans, and interobserver variability.[89] Image subtraction can overcome these issues, thus providing good visualization and quantification of active and negatively active (that is, shrunken or resolved) T2 lesions (Figure 3).[90] However, subtraction requires time-consuming post-processing steps, and is susceptible to artefacts. Long-interval T2-weighted sequences can be processed with automated subtraction, which has been used in a multicentre trial to provide greater power for assessing treatment efficacy than is possible with monthly contrast-enhanced T1-weighted imaging.[90,91] Application of automated subtraction in treatment trials or for treatment monitoring can improve cost-effectiveness and lower the risk of adverse effects associated with repeated contrast administration. Recent data have shown that automated identification of new and/or enlarged T2 lesions is robust, accurate and sensitive, thus supporting its use for evaluating treatment efficacy in clinical trials.[92]

Nonetheless, additional work is needed before these methods can be incorporated into clinical practice to assess MS activity. Proposed scoring methods to identify patients with a suboptimal treatment response on the basis of combined clinical and radiological measures at follow-up have shown considerable variation (Table 1). Moreover, these criteria have been developed almost exclusively in patients receiving different formulations of IFN-β; few data are available from patients undergoing treatment with other DMDs in clinical practice. Future MRI criteria for predicting treatment response should incorporate new imaging measures (for example, brain atrophy or spinal cord pathology), genetic factors and

Table 1 | MRI criteria for predicting treatment response

Criteria	Outcome measure	Results
Three or more active lesions in 1 year[134]	Disability progression over 3 years	OR 8.3 71% sensitivity 71% specificity
Three or more active lesions plus one or more relapse or ≥1 point confirmed EDSS score increase in 1 year[67]	Relapse rates and/or disability progression over 3 years	OR 3.3–9.8 for relapses OR 6.5–7.1 for progression
Modified Rio Score ≥2 and more than five new T2 lesions plus one relapse; or more than one relapse[79]	Relapse rates and/or disability progression over 4 years	24% sensitivity 97% specificity
One or more relapse and nine or more T2 lesions or a minimum of one CEL[80]	Relapse rates and/or disability progression over 4 years	34% sensitivity 90% specificity
One or more relapse, or at least one CEL[80]	Relapse rates and/or disability progression over 4 years	68% sensitivity 80% specificity
One or more CELs, or at least two new T2 lesions[80]	Relapse rates and/or disability progression over 4 years	61% sensitivity 83% specificity

All patients in these observational studies had relapsing–remitting multiple sclerosis treated with a formulation of IFN-β. Odds ratios refer to the probability that patients meeting the criteria will demonstrate the outcome measure, relative to patients who do not meet the criteria. Abbreviations: CEL, contrast-enhancing lesion; EDSS, Expanded Disability Status Scale.

laboratory biomarkers to enrich the predictive power for treatment response in individual patients, and should be validated in patients receiving DMDs other than IFN-β.

Statements and recommendations

- Baseline (pretreatment) brain MRI measures do not satisfactorily predict treatment response in clinical practice,[70] but scans within the first few months of treatment initiation can predict treatment response in patients receiving first-line DMDs[67,79–82]
- Follow-up brain MRI, including T2-weighted and contrast-enhanced T1-weighted sequences, should be performed 12 months after starting treatment and compared with a reference scan obtained after the treatment has taken effect[69]
- Timing of this reference scan should consider the precise time that treatment was started and the drug's mechanism of action; scans at 6 months after the start of treatment should be considered[69]
- New T2 lesion count requires high-quality, comparable MRI scans, and must be interpreted by highly qualified, trained readers to minimize observer variability[89]
- MRI subtraction facilitates recognition of changes in focal lesions over time, thereby increasing the power of serial imaging[91]
- Automated subtraction improves accuracy and sensitivity for identifying new and/or enlarged T2 lesions, although validation studies and technical improvements are required before this strategy can be incorporated into clinical practice[92]
- The available data do not suffice to support the use of brain volume or spinal cord measures for predicting treatment response in individual patients

Detection of adverse effects

The role of MRI in MS drug surveillance is becoming more important as the new generation of immunomodulatory and immunosuppressive drugs enter more widespread use. In general, MRI has three major tasks in this context: detection of persistent disease activity, comorbidities (such as vascular or neoplastic disorders) and adverse effects (including opportunistic infections).[7,93]

The crucial role of MRI in pharmacovigilance is made evident by the case of natalizumab, a recombinant humanized monoclonal antibody against α4-integrin.[94] This treatment for MS is highly effective, but is associated with progressive multifocal leukoencephalopathy (PML), a potentially life-threatening adverse effect. Imaging findings of natalizumab-associated PML are heterogeneous and can, therefore, be difficult to interpret. However, experienced readers who are fully informed of patient backgrounds can reliably detect natalizumab-associated PML via MRI,[95–97] even before patients manifest symptoms.[98] Detection of PML lesions at this asymptomatic or presymptomatic stage is associated with improved survival and functional outcome.[99]

Up to now, there have been no strict guidelines on how and when to perform MRI for safety monitoring in natalizumab-treated patients with MS. Factors such as lengthy treatment duration, past use of other immunosuppressive drugs, and the presence (and levels) of antibodies against the JC virus (JCV) have been associated with an increased risk of PML in these patients.[100–103] Therefore, the frequency of MRI scanning should be adjusted according to the individual's risk of PML.

Substantial evidence indicates that T2-FLAIR (fluid-attenuated inversion recovery) is the most sensitive sequence for detecting PML.[104] Diffusion-weighted imaging is highly sensitive for depicting acute demyelination, and can also aid differentiation of acute PML lesions from chronic and subacute demyelinating MS lesions.[104] Therefore, frequent MRI scanning using T2-FLAIR and diffusion-weighted sequences in combination with conventional T2-weighted images is recommended for screening patients at high risk of developing PML. In patients with MRI lesions suggestive of PML, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-immune reconstitution inflammatory syndrome (IRIS), particularly during follow-up.[95,105]

MRI-based monitoring for early PML detection is appropriate not only for patients taking natalizumab, but also for other DMDs, including alemtuzumab,[106] rituximab[107] and dimethyl fumarate.[108–110]

The value of MRI for treatment monitoring goes beyond PML detection. Other opportunistic infections leading to encephalitis (such as varicella zoster) can also develop in patients with MS, as has been shown during or after treatment with fingolimod, a sphingosine-1-phosphate receptor modulator approved for MS treatment.[111–114] In addition, serious paradoxical reactions, such as tumefactive demyelination or overwhelming inflammatory demyelination, can occur during fingolimod treatment.[115,116]

Given the growing number of immunosuppressive and immunomodulatory treatments for MS, MRI-based safety monitoring will become increasingly complex, as

Box 2 | Protocol for follow-up MRI in patients with MS

Regular brain MRI scans are essential for monitoring disease progression in patients with MS, but—in contrast to the diagnosis of MS—spinal imaging is not necessary for most patients. The frequency and make-up of each follow-up is determined by the needs of the individual patient.

Recommendations for routine follow-up

- Contrast-enhanced T1-weighted scans and T2-weighted scans can reveal inflammation and the development of new and/or enlarging lesions
- MRI subtraction techniques can facilitate the detection of new lesions across serial scans, but automated subtraction should be used with caution
- T2-weighted images, T2 fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging should also be used in patients at risk of serious treatment-related adverse effects, such as PML
- Follow-up scans should be conducted at least annually, and as often as every 3–4 months in patients who require enhanced pharmacovigilance

Recommendations for further clinical study

- Changes in total brain, grey matter and/or white matter volumes can predict disability, but these measures are difficult to obtain and interpret in the routine clinical setting, which limits their clinical relevance to standard patient care
- Magnetization transfer imaging, diffusion tensor imaging and proton magnetic resonance spectroscopy show promise for uncovering the mechanisms of MS pathogenesis, but these findings require further validation to confirm their clinical value
- As the availability of new MRI hardware (for example, 7 T MRI) increases, scanning protocols may need to be updated

Abbreviations: MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

well as more valuable. An example of this complexity can be seen in patients treated with natalizumab who switch to different drugs, such as fingolimod or alemtuzumab, owing to drug safety concerns. Evidence is accumulating that drug-related adverse effects can occur at the time an MS treatment is discontinued or even several months after a new treatment is started (so-called 'carry-over opportunistic infections').[117–119] Therefore, strict pharmacovigilance, including frequent MRI scanning, should be performed in patients who switch therapies, so as to detect resurgent MS disease activity and adverse effects such as opportunistic infections.

Statements and recommendations

- MRI should be included in drug surveillance programmes to screen for opportunistic infections,[103,114] unexpected disease activity (including paradoxical reactions),[82,115,116] and comorbidities[7,93]
- For natalizumab-treated patients with MS who are at high risk of PML (JCV seropositive, treatment duration ≥18 months), we recommend brain MRI screening every 3–4 months using an MRI protocol that includes FLAIR, T2-weighted and diffusion-weighted imaging[95–99,101,104]
- In patients at low risk of PML (JCV seronegative), we recommend brain MRI assessment once a year using the same MRI protocol[95–99,101,104]
- In patients at high risk of developing opportunistic infections who are switching DMDs, we recommend brain MRI at the time that the current treatment is discontinued and after the new treatment is started[117–119]
- Enhanced pharmacovigilance, including brain MRI every 3–4 months for up to 12 months, is required in patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate)[117–119]

Standardized follow-up MRI protocol

The use of MRI in the routine follow-up of patients with MS is less straightforward than in the diagnostic process, owing largely to the experimental nature of many of the techniques that have been used to measure disease progression. Here, we present a brief recommendation for a standard approach to patient monitoring, which is based on MRI techniques that have high clinical relevance (Box 2). These guidelines will require revisions as the use of advanced MRI techniques increases, and the availability of high-field-strength MRI widens.

Although follow-up MRI scans should be as consistent as possible with baseline or reference scans, fewer sequences are necessary than we have recommended for diagnosis.[10] The specific follow-up protocol strongly depends on the purpose of the scan (for example, treatment efficacy monitoring versus PML screening). To detect new or enlarging lesions, proton-density and/or T2-FLAIR and T2-weighted fast or turbo spin-echo sequences should be used. A gadolinium-enhanced T1-weighted sequence can increase confidence in the detection of lesions with high inflammatory activity. As with diagnostic scans, the delay between contrast adminstration and T1 acquisition—a minimum of 5 min—can provide an opportunity to perform proton density-weighted, T2-weighted and/or T2-FLAIR after contrast administration and before the T1 postcontrast acquisition. This approach optimizes the total scanning time. Diffusion-weighted scans should also be considered in patients at risk of PML.

Follow-up MRI should be conducted at least once every year in patients with MS, but patients at risk of serious treatment-related adverse events may need to be monitored more frequently, for example, every 3–4 months. Accurate positioning of follow-up and reference scans is essential for the accurate assessment of changes in lesion size and number over time. Algorithms that automatically position serial MRI scans are currently difficult to implement in routine clinical use, but might be useful in the near future.

All scans should be performed at a field strength of at least 1.5 T, though higher field strengths might reveal more new lesions. For 2D sequences, slice thickness should be no more than 3 mm with an in-plane spatial resolution of 1 × 1 mm (voxel size 3 × 1 × 1 mm). Voxels in 3D sequences should be 1 mm^3. Further technical details for the above sequences can be found in the first part of our consensus guidelines.[10]

Statements and recommendations

- Follow-up MRI scans typically require fewer sequences per session than do diagnostic scans, and can be completed in 20–25 min
- Routine monitoring should be conducted every 3–12 months, depending on patient characteristics such as disease duration, comorbidities and current treatment

- Several advanced techniques show promise for investigating MS pathology, and may need to be incorporated into future protocols

Future perspectives

The role of MRI in MS disease monitoring is gaining research interest as well as clinical importance. Treatment options and strategies for patients with MS are dynamically moving towards an individualized approach that includes conventional targets—immune modulation and immune suppression—and new targets such as neuroprotection and remyelination.[26,31,120] Therefore, we will need new MRI biomarkers that focus on additional and alternative aspects of MS pathology.

A promising source for a new biomarker is grey matter pathology, as correlations between cortical lesions and important clinical outcome measures, such as cognition, are stronger when grey matter and white matter are evaluated jointly.[121–126] Several MRI techniques, including double inversion recovery and phase-sensitive inversion recovery, have been used to detect, score and interpret cortical grey matter lesions, but these applications lack standardization.[127–129] Advanced, quantitative imaging techniques may also acquire a central role for evaluating the course of MS pathology in the near future. Standardization of these methods, particularly in multicentre settings, will be a challenge.

The use of MRI in the context of disease and treatment monitoring might benefit from a paradigm shift away from focal inflammatory lesions and whole-brain atrophy and towards certain clinically relevant anatomical structures, such as the thalamus, cortical grey matter and upper cervical spinal cord.[58,65,130] This shift will require greater implementation of new-generation high-field MRI systems for the detection and quantification of MS pathology, which have been investigated in relation to the diagnosis and differential diagnosis of MS.[131–133] Whether high-field MRI technology might also be of value for MS disease monitoring must be further evaluated, but it seems likely that these techniques, along with the new MRI markers they reveal, will have an important impact on MS disease monitoring in the future.

Future needs and recommendations

- Future research must identify new MRI markers of neuroinflammation and neuroprotection, particularly in the context of grey matter pathology (cortical and deep grey matter structures), remyelination and neuronal repair
- These new markers might require next-generation MRI technology, including new advanced pulse sequences, and enhanced hardware, such as new coils, multitransmit techniques and ultra-high field strengths
- Increased efforts are needed to implement and harmonize various advanced MRI techniques, and to standardize the acquisition and interpretation of MRI in patients with MS
- Systematic research is needed to assess the added value of alternative versus standard pulse sequences, MRI subtraction techniques and serial MRI scanning for disease and safety monitoring (including the most cost-effective follow-up frequency)

Conclusions

This Expert Consensus Document discusses the contribution of MRI to the monitoring of MS disease and treatment. The guidelines and recommendations provided are intended to aid decision-making regarding the MRI protocol and timing of follow-up scans, and the use of additional MRI techniques for prognostication and monitoring of patients with MS. Although this paper is based on the most recent data and our extensive clinical experience with MS treatments, we note that care for patients with MS is constantly influenced by new treatment strategies and new imaging approaches. Therefore, these guidelines should be periodically updated.

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Author contributions

M.P.W. and À.R. researched data for the article, and M.P.W., À.R., M.T., C.T., M.P.S., N.d.S., M.F., M.A.R. and F.B. wrote the article. All authors made substantial contributions to discussions of the content, and helped to review and/or edit the manuscript before submission.

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Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis

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ABSTRACT

SUMMARY: An international group of neurologists and radiologists developed revised guidelines for standardized brain and spinal cord MR imaging for the diagnosis and follow-up of MS. A brain MR imaging with gadolinium is recommended for the diagnosis of MS. A spinal cord MR imaging is recommended if the brain MR imaging is nondiagnostic or if the presenting symptoms are at the level of the spinal cord. A follow-up brain MR imaging with gadolinium is recommended to demonstrate dissemination in time and ongoing clinically silent disease activity while on treatment, to evaluate unexpected clinical worsening, to re-assess the original diagnosis, and as a new baseline before starting or modifying therapy. A routine brain MR imaging should be considered every 6 months to 2 years for all patients with relapsing MS. The brain MR imaging protocol includes 3D T1-weighted, 3D T2-FLAIR, 3D T2-weighted, post-single-dose gadolinium-enhanced T1-weighted sequences, and a DWI sequence. The progressive multifocal leukoencephalopathy surveillance protocol includes FLAIR and DWI sequences only. The spinal cord MR imaging protocol includes sagittal T1-weighted and proton attenuation, STIR or phase-sensitive inversion recovery, axial T2- or T2*-weighted imaging through suspicious lesions, and, in some cases, postcontrast gadolinium-enhanced T1-weighted imaging. The clinical question being addressed should be provided in the requisition for the MR imaging. The radiology report should be descriptive, with results referenced to previous studies. MR imaging studies should be permanently retained and available. The current revision incorporates new clinical information and imaging techniques that have become more available.

ABBREVIATIONS: CIS = clinically isolated syndrome; CMSC = Consortium of MS Centers; PML = progressive multifocal leukoencephalopathy

MR imaging of the brain and spinal cord is sensitive for detecting white matter lesions typical of MS. The current diagnostic criteria for MS[1] include specific MR imaging features (Table 1) to provide evidence for dissemination in space and/or time, allowing an earlier diagnosis of MS after a single clinical syndrome consistent with demyelination (clinically isolated syndrome [CIS]). The newer criteria have good sensitivity and specificity[2] compared with the prior clinical criteria.[3] However, white matter lesions are common in the general population with increasing age, and the MR imaging criteria should be used with caution in patients with atypical symptoms for MS or the onset of symptoms in patients older than 40 years of age. This recommendation is particularly important in the presence of factors known to cause T2 hyperintensities, including hypertension, smoking, diabetes, high cholesterol, and migraines.

MR imaging is also increasingly used to follow patients with a diagnosis of definite MS to determine progression of clinically silent disease activity and to monitor response to therapy. Gadolinium (contrast)–enhancing lesions and/or changes in T2 (hyperintense) lesions are accepted MR imaging biomarkers of new inflammation. New MR imaging activity occurs more frequently than new clinical symptoms (relapses).[4] The ability to monitor patients with MS with MR imaging is hampered by inconsistent protocols and image quality.

Recommendations for a standardized MR imaging protocol and clinical guidelines in MS were previously published.[5] These

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developed out of a series of meetings sponsored by the Consortium of MS Centers (CMSC), including radiologists and neurologists from academic and community-based MS practices and representatives of the American Academy of Neurology, the Radiological Society of North America, and the American Society of Neuroradiology. The goal of this article is to update the MR imaging protocol and clinical guidelines on the basis of advances in imaging technology and new clinical evidence of the role of MR imaging in the diagnosis and monitoring of MS.

Methods

Neurologists, radiologists, and imaging scientists with an expertise in MS from North America and Europe, representatives of the American Academy of Neurology, the Radiological Society of North America, the American Society of Neuroradiology, and, more recently, the National Institutes of Health and the North American Imaging in Multiple Sclerosis Cooperative updated the guidelines on the basis of new data, survey results, and expert opinion. Four imaging protocols, routine brain, progressive multifocal leukoencephalopathy (PML) surveillance, spinal cord, and orbits, were developed. Clinical guidelines on the recommended frequency of imaging in diagnosing and monitoring MS were updated.

Protocol 1: Brain MR Imaging. The brain MR imaging protocol (Table 2 and Fig 1) provides the minimum required sequence to aid in the diagnosis and monitoring of MS that can be performed on a variety of clinical scanners and includes 3D T1-weighted, 3D T2-FLAIR, 3D T2-weighted, and post-single-dose gadolinium-enhanced T1-weighted imaging, all with a nongapped section thickness of ≤3 mm, and a DWI sequence (≤5-mm section thickness). Additional sequences for non-MS pathology can be added, depending on the individual needs of the patient and local preferences.

Scans should be of good quality with adequate SNR and spatial resolution (in-section pixel resolution of ≤1 × 1 mm). Reconstruction (interpolation) is recommended at 0.5 mm. This recommendation may be limiting for some older scanners, particularly those operating at lower field strengths. One needs to be aware of the higher lesion-detection rates at 3T compared with 1.5T.[6] Lower field (ie, "open magnet") should only be used in extenuating circumstances.

Coverage should include the whole brain. Orientation of the axial sequences (acquisition of 2D sequences or reformatting of 3D sequences) should be along the subcallosal line (Fig 1) because consistent repositioning is essential for detecting changes across time.

Most scanners are capable of 3D acquisitions with ≤1.2-mm

Table 1: 2010 Revised McDonald diagnostic criteria for MS[a]

Minimum MRI Features for DIS (2 of 4 Criteria Required)
1 Infratentorial lesion
1 Juxtacortical lesion (touching the cortex)
1 Periventricular lesion (touching the ventricles)
1 Spinal cord lesion

Note:—DIS indicates dissemination in space; DIT, dissemination in time.
[a] MS diagnosis requires clinical and/or MRI evidence for CNS demyelination occurring in multiple locations (DIS) and with multiple events (DIT). The MRI criteria may support the clinical diagnosis of patients with MS with typical symptoms of CNS demyelination after the exclusion of alternative diagnoses. The DIT criterion can be met on MRI with an asymptomatic contrast-enhancing lesion on T1WI sequences (first or follow-up MRI) or newly active T2WI lesions on follow-up MRI. Lesions should be at least 3-mm in diameter and asymptomatic.

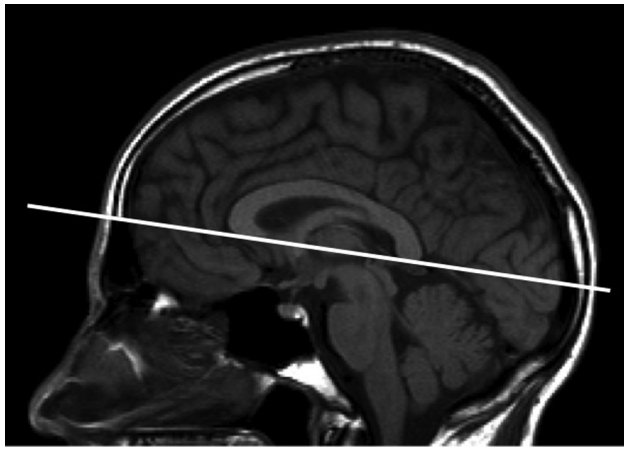

FIG 1. Orientation of axial oblique sequences. Orientation of axial oblique sequences should be along the subcallosal line as indicated by the solid line. Axial sections should be ≤3 mm with no gap.

Table 2: Standardized brain MRI protocol (diagnosis and routine follow-up of MS)

Parameters	Description
Field strength	Scans should be of good quality, with adequate SNR and resolution (in-sections, pixel resolution of ≤1 × 1 mm)
Scan prescription	Use the subcallosal plane to prescribe or reformat axial oblique sections (Fig 1)
Coverage	Whole-brain coverage
Section thickness and gap	≤3 mm, No gap (for 2D acquisition or 3D reconstruction)
Core sequences	Anatomic 3D inversion recovery–prepared T1 gradient echo (eg, 1.0- to 1.5-mm thickness)
	Gadolinium single dose, 0.1 mmol/kg given for 30 seconds[a]
	3D sagittal T2WI FLAIR[b] (eg, 1.0- to 1.5-mm thickness)
	3D T2WI [b] (eg, 1.0- to 1.5-mm thickness)
	2D axial DWI (≤5-mm sections, no gap)
	3D FLASH (non-IR prep) postgadolinium[b] (eg, 1.0- to 1.5-mm thickness)
	3D series would be typically reconstructed to 3-mm thickness for display and subsequent comparison for lesion counts
Optional sequences	Axial proton attenuation
	Pre- or postgadolinium axial T1 spin-echo (for chronic black holes)
	SWI for identification of central vein within T2 lesions

Note:—IR indicates inversion recovery.
[a] Minimum 5-minute delay before obtaining postgadolinium T1. The 3D sagittal FLAIR may be acquired immediately after contrast injection before the 3D FLASH series.
[b] If unable to perform a 3D acquisition, then perform 2D axial and sagittal FLAIR, axial fast spin-echo proton attenuation/T2, and axial post-gadolinium T1WI spin-echo at ≤3-mm section thickness.

Table 3: PML surveillance brain MRI protocol

Parameters	Description
Field strength	Scans should be of good quality, with adequate SNR and resolution (in-section pixel resolution of ≤1 × 1 mm)
Scan prescription	Use the subcallosal plane to prescribe or reformat axial oblique sections (Fig 1)
Coverage	Whole-brain coverage
Sequences	3D sagittal T2WI FLAIR[a]
	2D axial DWI (5-mm-thick, no gap)
Section thickness and gap	≤3 mm, No gap (for 2D acquisition or 3D reconstruction)

[a] If unable to perform a 3D acquisition, then perform 2D axial FLAIR at ≤3-mm section thickness.

isotropic voxels.[7] The data can be reformatted to achieve 3-mm axial and/or sagittal sections for clinical readout. If a 2D acquisition is used, the section thickness should be ≤3 mm and there should be no gap between sections. 3D FLAIR may be equivalent or superior to T2-weighted imaging for posterior fossa lesions. It is recommended that a 3D T2 or a 3-mm axial fast/turbo spin-echo proton attenuation/T2 sequence be acquired for posterior fossa lesion detection as a backup.

The brain MR imaging sequences include a sagittal FLAIR (the 3D acquisition is usually acquired in the sagittal plane) for the detection of MS lesions in the corpus callosum. Although these lesions can be identified on axial images, the sagittal plane provides greater ease of visualization of these, as well as juxtacortical lesions (ie, white matter lesions touching the cortex) and the oval perivenular configuration of lesions.

A thin-section (≤1.5-mm thickness) 3D inversion recovery–prepared, T1-weighted, spoiled gradient-echo sequence is useful for volumetric analysis, which is likely to play an important role in the future. The 3D inversion recovery sequence should be acquired before contrast. This sequence also enables confirmation of juxtacortical and infratentorial lesions. Chronic T1-weighted "black hole" monitoring as a marker of severe axonal injury has only been validated on 2D spin-echo sequences. Because nearly all hyperintense lesions apparent on T2-weighted sequences are hypointense on 3D inversion recovery T1-weighted scans, the specificity of T1 black holes is lost and clinical interpretation requires caution.[8]

The protocol includes a postgadolinium contrast 3D FLASH (non-inversion recovery prep) or axial T1-weighted spin-echo images. Although 3D gradient echo–based T1-weighted imaging could be used as a replacement for T1 spin-echo for identifying postgadolinium contrast enhancement, whether such sequences are less sensitive[9] remains an open question.

Axial DWI (5 mm) is recommended for detecting non-MS pathology, including acute ischemia/infarction and the earlier detection of PML (see below).

The 3D or 2D FLAIR and/or T2-weighted images can be acquired during the minimum 5-minute delay that is required before the postcontrast T1-weighted image. Phased array coils may significantly speed up acquisition time.

Proton attenuation and precontrast 2D spin-echo T1-weighted imaging are considered optional. Subtle lesions can be confirmed on proton attenuation imaging, though the sensitivity of 3D FLAIR may obviate this confirmation.[10]

Gadolinium contrast detects the breakdown of the blood-brain barrier that occurs with new lesion development and reactivation of old lesions. The average duration of enhancement for individual brain lesions is 3 weeks,[11] with most enhancing for 2–6 weeks. Rarely, MS lesions in the brain show persistent enhancement for >3 months with single-dose gadolinium. A standard dose of gadolinium (0.1 mmol/kg) given for 30 seconds and a minimum 5-minute delay before acquiring the postcontrast T1-weighted imaging are recommended. "Triple dose" and longer delays of up to 15 minutes for the postcontrast T1-weighted imaging may detect more lesions but are not necessary for routine clinical practice. Reports of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in patients with preexisting significant renal impairment have resulted in many centers requiring a recent laboratory assessment of renal function, such as an estimated glomerular filtration rate. Macrocyclic chelates have been recommended by several radiologic societies to minimize this risk.[12,13]

Most newly enhancing lesions will leave residual T2 hyperintensity after the enhancement resolves.[14] Detecting new or enlarging T2 lesions compared with a previous study would also indicate new inflammatory activity even in the absence of gadolinium enhancement. However, to reliably detect new lesions, a standardized MR imaging protocol with similar orientation and other parameters is important. Gadolinium can also be helpful for ruling out alternative diagnoses such as tumors (persistent enhancement) or leptomeningeal disease such as neurosarcoidosis[15,16] or infection.

Protocol 2: PML Surveillance Brain MR Imaging. PML is a devastating complication that is rarely seen with some disease-modifying therapies (Table 3). The risk is increased in patients with detectable John Cunningham virus serum antibodies. MR imaging detection of PML in the presymptomatic phase improves outcome and survival.[17] An abbreviated PML surveillance protocol includes 3D (or 2D) FLAIR and DWI sequences.[18] Postcontrast T1 adds little diagnostic value to PML surveillance because <50% of early PML lesions show contrast enhancement.[19] Typical PML lesion appearance includes subcortical lesions (48% occur in the frontal lobes) that are hyperintense on T2/FLAIR and hypointense on T1-weighted imaging, with ill-defined borders toward the white matter and sharp borders toward the gray matter and high signal intensity on DWI (absent in about 40% of patients with presymptomatic PML). Lesions can involve the deep gray matter (thalamus and dentate nuclei). Contrast enhancement can be patchy, nodular, or speckled.[18,19]

Protocol 3: Spinal Cord MR Imaging. As a minimum, coverage should include the cervical cord (Table 4) because clinically silent MS lesions are more common and better visualized there. It may not be necessary to examine the thoracic cord routinely unless there are clinical symptoms and/or signs at that level. Two sequences are recommended for the detection of subtle lesions, including a sagittal T2-weighted and a proton attenuation, STIR, or

Table 4: Spinal cord MRI protocol

Parameter	Description
Field strength	Scans should be of good quality, with adequate SNR and resolution (in-section pixel resolution of ≤1 × 1 mm) Closed magnets (large bore for patients with claustrophobia) preferred
Coverage	Cervical cord coverage[a]
Core sequences	Sagittal T2 Sagittal proton attenuation, STIR, or PSTI-IR Axial T2 through lesions
Section thickness and gap	Sagittal: ≤3 mm, no gap Axial: 5 mm, no gap
Optional sequences	Axial T2 through complete cervical cord Gadolinium[b] and postgadolinium sagittal T1 Sagittal T1

Note:—PSTI-IR indicates phase-sensitive T1 inversion recovery.

[a] Thoracic and conus coverage recommended if symptoms localize to this region to rule out an alternate diagnosis.

[b] Minimum 5-minute delay before obtaining postgadolinium T1. Additional gadolinium does not need to be given for a spinal cord MRI if it follows a contrast brain MRI study.

Table 5: Clinical guidelines for brain and spinal cord MRI in MS

Guidelines
Baseline studies for patients with a CIS and/or suspected MS
Brain MRI protocol with gadolinium at baseline and
Spinal cord MRI if transverse myelitis, insufficient features on brain MRI to support diagnosis, or age older than 40 years with nonspecific brain MRI findings
A cervical cord MRI performed simultaneously with the brain MRI would be advantageous in the evaluation of patients with or without transverse myelitis and would reduce the number of patients requiring a subsequent MRI appointment
Orbital MRI if severe optic neuritis with poor recovery
Timing of a follow-up brain MRI protocol for patients with a CIS and/or suspected MS to look for evidence of dissemination in time
6–12 Months for high-risk CIS (eg, ≥2 ovoid lesions on first MRI)
12–24 Months for low-risk CIS (ie, normal brain MRI findings) and/or uncertain clinical syndrome with suspicious brain MRI features (eg, RIS)
Timing of brain MRI protocol with gadolinium for patients with an established diagnosis of MS
No recent prior imaging available (eg, patient with MS transferring to a new clinic)
Postpartum to establish a new baseline
Prior to starting or switching disease-modifying therapy
Approximately 6 months after switching disease-modifying therapy to establish a new baseline on the new therapy
Every 1–2 years while on disease-modifying therapy to assess subclinical disease activity
Unexpected clinical deterioration or reassessment of original diagnosis[a]
Timing of PML surveillance brain MRI protocol
Every 12 months for patients negative for serum JC virus antibody
Every 3–6 months for patients positive for serum JC virus antibody and ≥18 months on natalizumab[b]

Note:—JC indicates John Cunningham; RIS, radiologic isolated syndrome.

[a] Routine spinal cord follow-up not required unless syndrome is predominately recurrent transverse myelitis.

[b] The brain MRI protocol for monitoring patients on disease modifying therapies includes the PML surveillance sequences.

T1-weighted inversion recovery sequence with phase-sensitive reconstruction (section thickness, ≤3 mm).[20] Axial T2 or T2* and postcontrast axial T1 through the lesions is recommended (section thickness of 5 mm, no gap). A sagittal T1 is of limited value for characterizing intramedullary disease. When spinal cord imaging is performed at the same time as brain imaging with gadolinium, no additional contrast is required.

Protocol 4: Orbit MR Imaging. Imaging of the orbit may be clinically indicated to confirm optic neuritis and rule out compressive lesions. Unusual enhancement patterns of the optic nerve and/or sheath might suggest an alternate diagnosis such as sarcoidosis or neuromyelitis optica.[21] The recommended sequences include a coronal STIR or fat-suppressed T2 and a postgadolinium fat-suppressed T1 with a section thickness of ≤2 mm, with coverage through the optic chiasm.

Clinical Guidelines: Diagnostic Imaging for Suspected MS

While MR imaging is not absolutely required for the clinical diagnosis of MS (Table 5), it provides important information.[22] A brain MR imaging with and without gadolinium is recommended for patients suspected of having MS or with an established diagnosis of MS who are new to a clinical practice and do not have recent imaging available for review. A cervical cord MR imaging at the same time would be advantageous in the diagnostic evaluation of patients with or without transverse myelitis and would reduce the number of patients requiring a subsequent MR imaging appointment. Patients suspected of having MS include those with a CIS of optic neuritis, partial transverse myelitis, or brain stem syndromes. Patients with CIS with a brain MR imaging with ≥2 characteristic lesions (≥3 mm in diameter) have a high risk for MS.[23] One-third of patients with CIS (not treated with corticosteroids) will have asymptomatic gadolinium-enhancing lesions and will meet the 2010 McDonald diagnostic criteria for definite MS.[24] Detection of new T2 or gadolinium-enhancing lesions on a follow-up brain MR imaging can be sufficient evidence to fulfill dissemination in time and/or space criteria (Table 1). The recommended timing of the follow-up brain MR imaging is 6–12 months. The proportion of patients with high-risk CIS (younger

Table 6: Recommendations for communication

Recommendations
The clinical requisition for brain MRI should include
Requesting the CMSC or standardized brain MRI protocol
Indicating the purpose of the study
Diagnostic study for CIS or MS (indicate date of symptom onset)
Treatment-monitoring study (indicate if on disease-modifying therapy)
PML surveillance study (indicate if high- or low-risk)
Unexpected clinical decline or reassessment of diagnosis
Date and location of most recent MRI study (encourage patient to bring a copy of outside images on portable media at the time of MRI appointment)
The radiology report should include
For a diagnostic MS study
Number of gadolinium-enhancing T1 lesions (eg, 0, 1, 2, 3, 4, ≥5)
Comparison with previous studies for the number of new T2 lesions (eg, 0, 1, 2, 3, 4, ≥5)
The presence of juxtacortical (touching the cortex), periventricular (touching the ventricles), infratentorial, or spinal cord lesions
The report should avoid a summary statement like "McDonald diagnostic criteria met"
The interpretation should indicate whether findings are typical, atypical, or not consistent with MS and should provide a differential diagnosis if appropriate
For a follow-up MS study
Number of gadolinium-enhancing T1 lesions (eg, 0, 1, 2, 3, 4, ≥5)
Comparison with previous studies for the number of new T2 lesions (eg, 0, 1, 2, 3, 4, ≥5)
Qualitative assessment of
Overall T2 lesion-burden severity (eg, mild, moderate, severe)
Comparison with previous studies for overall worsening of T2 lesion burden and atrophy
For a PML surveillance study
Comparison with previous studies for new T2 lesions, hyperintense lesions on DWI
Presence of PML suspicious features

than 50 years of age) who develop new lesions by 3, 6, and 12 months is 22%, 51%, and 74%, respectively.[25] By 12–18 months, most patients with high-risk CIS will meet the diagnostic criteria for MS by developing new MR imaging lesions and/or new clinical symptoms.[26] Additional MRIs can be performed according to clinical judgment. Some experts recommend an annual brain MR imaging in patients with CIS with normal brain MR imaging findings for 1–2 years or at the time of development of new symptoms consistent with demyelination.[23,27,28]

Patients suspected of having MS also include those with milder or atypical symptoms or incidental abnormalities on MR imaging that are strongly suspicious for MS (radiologic isolated syndrome).[29] The presence of a spinal cord lesion on MR imaging may be helpful in estimating the risk of conversion to definite multiple sclerosis.[30] A 5-year prospective study of 451 patients with radiologic isolated syndrome demonstrated that the risk of conversion to MS was 34%.[31] In addition to other paraclinical tests such as evoked potentials and CSF analysis, a follow-up MR imaging may support the diagnosis of MS by demonstrating new lesion development in patients suspected of having MS.

In patients with equivocal brain MR imaging findings (ie, not meeting dissemination in space criteria), the detection of lesions on spinal cord imaging can provide additional evidence for disease dissemination in space. Spinal cord lesions have greater specificity for demyelinating disease.[31,32] Nonspecific white matter lesions are extremely uncommon in the spinal cord, in contrast to their frequent occurrence in the brain.[33] Patients may present with a more severe demyelinating or inflammatory syndrome, including tumefactive lesions or acute complete transverse myelitis. A follow-up MR imaging would provide evidence of lesion improvement or resolution supporting an inflammatory process and/or the detection of new lesions that could aid in the differential diagnosis.[15,34]

Spinal cord imaging, in addition to brain imaging, is recommended if the symptoms involve the spinal cord such as partial transverse myelitis, complete transverse myelitis, or a progressive myelopathy suspicious for primary-progressive MS. Patients with progressive MS may have a chronic, diffuse, extensive abnormal spinal cord signal, though most do not. The detection of a longitudinally extensive spinal cord lesion (≥3 segments) with central cord predominance and mass effect in a patient with acute transverse myelitis is suggestive of neuromyelitis optica.[21] The longitudinally extensive involvement of these distinctive lesions is often transient.

Clinical Guidelines: Follow-Up of Established MS

The 4 common scenarios for requesting a brain MR imaging for patients with an established diagnosis of MS are the following: new baseline evaluation (previous MR imaging unavailable, unacceptable quality, or a long interval since the last MR imaging), routine follow-up for clinically silent disease activity while monitoring treatment response, PML surveillance, and unexpected clinical deterioration or re-evaluation of the diagnosis of MS (Table 6). A baseline spinal cord MR imaging may also be useful, depending on the clinical symptoms.

MR imaging is recommended before the initiation or modification of disease-modifying therapy and approximately 6 months after a treatment switch to allow sufficient time for the new therapy to reach its therapeutic potential. Determining ongoing radiologic stability is based on the presence or absence of new lesions (T2 or contrast-enhancing T1) relative to a posttreatment MR imaging.[35]

MR imaging is the most sensitive tool currently available for monitoring inflammatory disease activity in MS. Clinical assessments far underestimate disease activity and burden compared with MR imaging. A follow-up MR imaging is useful for patients on a disease-modifying therapy to determine the response of subclinical disease activity to treatment. Continued or worsening of MR imaging disease activity while on a disease-modifying therapy may prompt a change in therapy. There is evolving evidence that ongoing MR imaging activity can be indicative of a suboptimal therapeutic response.[36-41]

Many new lesions may be clinically silent, particularly when they occur outside the more functionally eloquent regions of the CNS (spinal cord, optic nerve). However, as more lesions accumulate in the CNS, studies demonstrate a clear relationship between the severity of cognitive dysfunction and lesion burden, even in patients with good mobility. CNS damage also occurs in brain tissue that appears normal on standard conventional imaging (normal appearing brain tissue). This slow, evolving damage can be monitored by nonconventional advanced MR imaging techniques that are mainly restricted to the research realm. New T2 or gadolinium-enhancing lesions are associated with progressive changes in normal appearing brain tissue and global brain atrophy.[42]

The frequency of periodic MR imaging to assess subclinical disease activity will vary depending on the patient's clinical course and other clinical features. For relapsing forms of MS, a follow-up MR imaging should be considered annually for at least the first 2 or 3 years after starting therapy or switching disease-modifying therapy. More frequent surveillance may be indicated in clinically aggressive cases or unusual patterns of MR imaging lesions (eg, tumefactive MS). Clinical judgment and experience may be critical in these settings. While guidelines on a tolerable threshold for new lesion activity that warrants a change in therapy have been proposed,[43,44] individual factors will impact the clinician's decision on the frequency of MR imaging monitoring. The frequency of MR imaging may be higher during the early years for patients with CIS and early relapsing-remitting MS, particularly when patients are on treatment. Fewer MR imaging scans are required in later stages of the disease (secondary-progressive MS) or in primary-progressive MS in which MR imaging activity is low and no effective treatments are as of yet available.[45] Nonetheless, multiple new T2 or contrast-enhancing lesions on surveillance scans in conjunction with the clinical picture, even in primary-progressive MS,[45] should alert the clinician to re-evaluate treatment strategies.

The PML surveillance recommendations by using a shorter protocol depend on John Cunningham virus serum antibody status, length of exposure to natalizumab, and the use of prior immunosuppressive therapy.[46] Higher risk patients (positive for John Cunningham virus serum antibodies) with >18 months of natalizumab exposure should have the PML surveillance MR imaging protocol performed every 3–6 months.[18] Any clinical change suspicious for PML should prompt an urgent MR imaging.

Indications for an unplanned follow-up brain MR imaging in patients with an established diagnosis of MS include the re-assessment of the original diagnosis or to clarify the cause of clinical deterioration that is not otherwise evident by clinical assessment (eg, stroke or tumor).

A spinal cord MR imaging may be indicated when there is significant clinical worsening with few changes on brain MR imaging or to rule out an alternative cause for progressive myelopathy, such as cervical spondylosis or a tumor. Routine follow-up with spinal cord imaging may be useful in rare cases of recurrent transverse myelitis to assess response to therapy or new disease activity.

Recommendations for Communication and Storage

The requisition should ask for standardized brain and/or spinal cord imaging and indicate the clinical question being addressed and include relevant clinical history (eg, CIS localization and symptom duration), current MS disease-modifying therapy, recent high-dose corticosteroids, and date and place of any previous MR imaging (Table 6).

The radiology report should use standardized terminology and include a description of salient findings. These include new T2 or contrast-enhancing T1 lesion numbers and the presence/absence of juxtacortical, periventricular, infratentorial, and spinal cord lesions. The report should avoid a summary statement like "McDonald diagnostic criteria met," because this requires clinical details that may not be available at the time of the radiologic review. The interpretation should indicate whether the findings are typical, atypical, or not consistent with MS, and the radiologist should provide a differential diagnosis, if appropriate. In patients with definite MS, a qualitative assessment of brain volume (atrophy) and overall T2 lesion burden and a comparison with previous studies for new lesion activity and atrophy are useful (Table 6). MR imaging studies should be stored in a standard readable format (DICOM), retained permanently, and available. Patients are encouraged to keep copies of their own studies and have these available if a follow-up MR imaging is performed at a different imaging center.

CONCLUSIONS

The goal of the original guidelines was to provide clinicians with a standardized MR imaging protocol that would be suitable for the initial diagnosis and monitoring of changes with time. The protocol was designed to provide the optimum amount of information that could be acquired within a routine clinical MR imaging setting. The current revision incorporates feedback from centers using the previous protocol and input from radiologists with expertise in MS. 3D FLAIR and 3D T2-weighted imaging are already being introduced into clinical practice. These techniques can provide potentially higher quality data (higher resolution, seamless reformatting) and should be comparable with the core 2D approaches. The methodologies for quantification of advanced imaging techniques, such as magnetization transfer imaging, MR spectroscopy, diffusion tensor imaging, and myelin water fraction imaging, require further standardization before their routine clinical use can be recommended. Methods sensitive to gray matter pathology (double inversion recovery and phase-sensitive T1 inversion recovery sequences) are being developed but are still currently investigational. An imaging challenge for the next decade is the continued translation of research methodologies into useful and reliable clinical tools for lesion identification, quantification of T2 lesion burden, and brain and spinal cord atrophy measures.

The revised guidelines provide consensus recommendations for the use of brain and spinal cord MR imaging and the use of gadolinium in the diagnosis of patients with MS. The challenge during the past decade was in reaching a consensus on the frequency of routine imaging to monitor patients with MS. The evidence supporting this role remains incomplete. However, there is consensus that MR imaging provides useful information about subclinical inflammatory activity in the early phase of the disease. It is reasonable for physicians to take these arguments for and against routine MR imaging into consideration when they individualize patient care.

During the past 3 decades, the clinical application of MR imaging in MS and the advances in imaging quality and speed have been remarkable. We anticipate that these guidelines will require future revision as MR imaging technology and our knowledge of MS continue to improve.

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Elizabeth Fisher—*RELATED*: *Consulting Fee or Honorarium*: CMSC, *Comments:* received an honorarium for participating in the CMSC MRI guidelines–development meeting; *Support for Travel to Meetings for the Study or Other Purposes*: CMSC, *Comments*: received travel support to participate in the CMSC MRI guidelines–development meeting; *UNRELATED*: *Consultancy:* Biogen, Genzyme, Novartis, *Comments*: received payments for consultant work; *Employment*: Biogen (employed as of January 5, 2015). David E. Jones—*RELATED*: *Consulting Fee or Honorarium*: CMSC; *Support for Travel to Meetings for the Study or Other Purposes*: CMSC; *UNRELATED*: *Consultancy*: Genzyme, Biogen Idec, Novartis, *Comments*: Although most of the money went to University of Virginia for these activities, I have received personal compensation for some consulting activities with these 3 companies in the past 3 years; *Grants/Grants Pending*: National Multiple Sclerosis Society,* Biogen Idec,* *Comments*: Site Principal Investigator for clinical trial with vitamin D; will be site Principal Investigator for Natalizumab as an Efficacy Switch in Participants with Relapsing Multiple Sclerosis After Failure on Other Therapies (ESCALATE); *Payment for Lectures (including service on Speakers Bureaus)*: Program of All-inclusive Care for the Elderly, *Comments*: 1 lectured in 2014 ($500); *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: Multiple Sclerosis Association of America. Jiwon Oh—*RELATED*: *Grant*: Multiple Sclerosis Society of Canada*; *UNRELATED*: EMD Serono, Biogen Idec, Roche, Genzyme; *Grants/Grants Pending*: Biogen Idec,* Genzyme*; *Payment for Lectures (including service on Speakers Bureaus)*: Teva, EMD Serono, Genzyme, Biogen Idec; *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: Genzyme, EMD Serono. David S. Reich—*UNRELATED*: *Payment for Development of Educational Presentations*: University of Pennsylvania (grand rounds). Nancy Richert—*UNRELATED*: *Employment*: Biogen; *Stock/Stock Options*: As a Biogen employee, I received restricted stock options; *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: Biogen pays my travel and accommodations for attending national meetings (eg, American Academy of Neurology, American Society of Neuroradiology, European Committee for Treatment and Research in Multiple Sclerosis). Kottil Rammohan—*UNRELATED*: *Consultancy*: Novartis, Genentech, Genzyme, Biogen Idec, EMD Serono, Teva Neurosciences; *Grants/Grants Pending*: Novartis,* Genentech,* Genzyme,* EMD Serono,* Biogen Idec,* Teva Neurosciences*; *Payment for Development of Educational Presentations*: Mallinckrodt; *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: CMSC. Omar Khan—*UNRELATED*: *Consultancy*: Teva, Biogen Idec, Genzyme, Novartis; *Grants/Grants Pending*: Wayne State University. Ernst-Wilhelm Radue—*UNRELATED*: *Board Membership*: Novartis,* Biogen*; *Consultancy*: Novartis, Biogen, Bayer Schering, Merck Serono, Genzyme, Synthon, MorphoSys; *Payment for Lectures (including service on Speakers Bureaus)*: Novartis, Biogen, Bayer Schering, Genzyme. Corey Ford—*RELATED*: *Grant*: Teva Neuroscience,* *Comments*: research grant for glatiramer acetate clinical trials including 20+ year-long term follow-up study; *Consulting Fee or Honorarium*: Teva Neuroscience, *Comments*: In the past few years, I have consulted with Teva for scientific/medical issues related to MS disease-modifying therapies, including glatiramer acetate; *Support for Travel to Meetings for the Study or Other Purposes*: Teva Neuroscience, *Comments*: travel to meetings for presentation of data and consulting; *Provision of Writing Assistance, Medicines, Equipment, or Administrative Support*: Teva, *Comments*: Teva staff participated in drafting this article and providing data from a data base maintained in multiple clinical trials of glatiramer acetate. I made substantive contributions to the writing, editing, proofing and verification of the content; *UNRELATED*: *Consultancy*: Novartis, Biogen Idec, *Comments*: I participated in several consulting meetings during the past 3 years. As with Teva, these were advisory-/medical-focused. I do not participate in Speakers Bureaus and all potential conflicts of interest such as these have been reported to the University of New Mexico Health Sciences Center Conflicts of Interest Committee for review and management; *Grants/Grants Pending*: multiple industry sponsors,* *Comments*: We perform 8–10 clinical trials each year for manufacturers of MS disease-modifying drugs. All are paid to the institution and conducted under appropriate compliance and reporting guidelines; *Payment for Development of Educational Presentations*: CMSC, *Comments*: I have received compensation for the creation of Continuing Medical Education materials for the CMSC in the field of MS clinical care. June Halper—*UNRELATED*: *Consultancy*: Biogen, *Comments*: Delphi study group. David Li—*UNRELATED*: *Board Membership*: Opexa Therapeutics (Data Safety Advisory Board); *Consultancy*: Vertex Pharmaceuticals, *Comments*: drug-development testing; *Grants/Grants Pending*: Genzyme,* Hoffman-La Roche,* Merck Serono,* Nuron,* Perceptives,* Sanofi-Aventis,* *Comments*: I am Director of the University of British Columbia MS/MRI Research Group, which has been contracted to provide central MRI analysis for therapeutic trials in multiple sclerosis. *Money paid to the institution.

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