



**Health Evidence Review
Commission's**

**Evidence-based Guidelines
Subcommittee**

June 6, 2013

**Meridian Park Hospital
Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR 97062**

AGENDA

EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)

June 6, 2013

2:00pm - 3:30pm

Meridian Park Hospital

Community Health Education Center Room 117B&C

19300 SW 65th Avenue, Tualatin, OR 97062

(All agenda items are subject to change and times listed are approximate)

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Wiley Chan
2	2:05 PM	Review of August minutes	Wiley Chan
3	2:10 PM	Coverage Guidance Evidence Algorithm revision	Cat Livingston
4	2:15 PM	VBBS report on Coverage Guidances	Cat Livingston
5	2:20 PM	<u>Continue review of Coverage Guidances:</u> Prenatal genetic testing	Cat Livingston Alison Little
6	2:45 PM	<u>Continue review of Coverage Guidances:</u> Treatment of attention hyperactivity deficit disorder in children.	Cat Livingston Alison Little
7	3:20 PM	Confirmation of next meeting September 12, 2013	Wiley Chan
8	3:25 PM	Next Topics	Cat Livingston
9	3:30 PM	Adjournment	Wiley Chan

Public comment will be taken at the time of topic discussion..

Section 2

Minutes

MINUTES

Evidence-based Guidelines Subcommittee

Meridian Park Room
Community Health Education Center, Room 117 B&C
19300 SW 65th Avenue, Tualatin, OR 97062
April 4, 2013
2:00pm - 5:00pm

Members Present: Wiley Chan, MD, Chair; Vice-Chair; Vern Saboe, DC (by phone); Beth Westbrook, PsyD; Irene Crowell, RPh; Leda Garside, RN (by phone); Som Saha, MD, MPH; Eric Stecker, MD.

Members Absent: Steve Marks, MD, Bob Joondeph, JD

Staff Present: Darren Coffman; Cat Livingston, MD, MPH; Jason Gingerich.

Also Attending: Alison Little, MD and Shannon Vandegriff (CEbP); Jessie Little (ASU); Denise Taray (DMAP), Yvonne Gordon (March of Dimes), Duncan Neilson (Legacy Health), Joanne Rogovoy (March of Dimes), Cori Feist (OHSU), Paige Hatcher (OHSU).

Roll Call/Minutes Approval/Staff Report

The meeting was called to order at 2:00 p.m. and roll was called. Minutes from the 2/7/2013 EbGS meeting were reviewed and approved without changes by a vote of 5-0 with Saha and Saboe not present.

Livingston reported on the coverage guidances previously referred to HERC but which were reviewed by the Value-based Benefits Subcommittee (VbBS) at its March 2013 meeting. The VbBS made minor modifications to the Cervical Cancer Screening Coverage Guidance and added a table which will be used in the Prioritized List. The subcommittee expressed no objections to the changes.

The VbBS made no changes to the Coverage Guidance for the Management of Acute Recurrent Otitis Media, but is recommending guideline note changes to the Prioritized List based on the coverage guidance.

The coverage guidances on Coronary Artery Calcium Scoring and Coronary Computed Tomography Angiography were also reviewed by VbBS, and recommended no changes to the coverage guidances or the Prioritized List.

Action: HERC staff will post the approved minutes and updated Coverage Guidance for Cervical Cancer Screening on the website as soon as possible.

➤ **Topic: Induction of Labor (Review Public Comment)**

Discussion: Livingston introduced the topic. She explained that two national groups have come out with recommendations not to schedule non-medically-indicated inductions between 39 and 41 weeks of gestation unless the cervix is favorable, and mentions these as a part of the policy landscape that committee members should be aware of. This subject is relevant to the largest question remaining for the subcommittee. Chan said that in his mind it is more of an implementation concern, as providers on the front line can face multiple conflicting recommendations from various bodies.

Alison Little reviewed the expert comment disposition and public comment disposition from the meeting materials.

Livingston reviewed the first line of the revised GRADE framework in the coverage guidance, noting where the recommendation now varies according the favorability of the cervix for delivery. Based on evidence, staff has changed the recommendation from a weak recommendation against coverage to a weak recommendation for coverage in women with a favorable cervix, and a weak recommendation against coverage with an unfavorable cervix. After discussion, the subcommittee agreed with the change to the coverage recommendation but requested that staff change the coverage guidance to indicate that the resource allocation is more costly with an unfavorable cervix and less costly with a favorable cervix.

Stecker asked Neilson whether the Bishop score is evidence based. Neilson said it is, as there is literature associating a higher score with lower time to deliver and less frequency of cesarean section. Little said that in the MED report a number of studies look at cervical status, specifically whether the cervix required ripening, which is essentially the same as cervical favorability. In nulliparous women a cervix which required ripening definitely increases the risk of cesarean section.

Chan asked whether a Bishop score greater than or equal to 6 is an agreed-upon cut point. Neilson said that there is some variation in the literature. Everyone would agree that less than six is not favorable and some studies would say seven is not favorable. Some hospitals have a higher threshold. After discussion the subcommittee agreed not to change the recommendation in the meeting materials, in the absence of clear evidence for a higher threshold, and to change the language in the coverage recommendation to “(for example, with a Bishop score ≥ 6)” and “(for example, a Bishop score < 6)”.

Livingston reviewed the changes to the coverage for cholestasis of pregnancy. The change to a weak recommendation was made for consistency with the GRADE framework, because it is based on a single case control study

Westbrook noted a typographical error (“an favorable cervix”) which will be corrected as well. The subcommittee then voted to refer the coverage guidance with the changes discussed above.

Actions: By a vote of 7-0, the subcommittee referred the draft coverage guidances, as amended, to VbBS and HERC.

HERC COVERAGE GUIDANCE

Induction of labor is recommended for coverage for the following indications (*strong recommendation*):

- Gestational age beyond 41 weeks 0 days
- Prelabor rupture of membranes, term
- Fetal demise
- Preeclampsia, term (severe or mild)
- Eclampsia
- Chorioamnionitis

Induction of labor is recommended for coverage for the following indications (*weak recommendation*):

- Diabetes, pre-existing and gestational
- Placental abruption
- Preeclampsia, preterm (severe or mild)
- Severe preeclampsia, preterm
- Cholestasis of pregnancy
- Preterm, prelabor rupture of membranes;
- Gastroschisis
- Twin gestation
- Maternal medical conditions (e.g., renal disease, chronic pulmonary disease, chronic hypertension, cardiac disease, antiphospholipid syndrome)
- Gestational hypertension
- Fetal compromise (e.g. isoimmunization, oligohydramnios)
- Intrauterine growth restriction/Small for gestational age, term
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with a favorable cervix (for example, with a Bishop score ≥ 6)

Induction of labor is not recommended for coverage for the following indications (*weak recommendation*):

- Macrosomia (in the absence of maternal diabetes)
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with an unfavorable cervix (for example, a Bishop score <6)
- Intrauterine growth restriction/Small for gestational age, preterm (without other evidence of fetal compromise)

Induction of labor is not recommended for coverage for the following indications (*strong recommendation*):

- Elective purposes <39 weeks (without a medical or obstetrical indication)

➤ **Topic: Neuroimaging for Headache**

Discussion: Little reviewed the public comment staff received from a CCO medical director, regarding making the language around “neck stiffness” to something more objectively defined. A variety of language options were discussed and the subcommittee approved the staff recommendation to change the language to “nuchal rigidity.”

Actions: The subcommittee approved the draft coverage guidance as presented in the meeting materials by a vote of 6-0 with Saboe not present.

HERC COVERAGE GUIDANCE

Neuroimaging is not recommended for coverage in patients with a defined tension or migraine type of headache, or a variation of their usual headache (e.g. more severe, longer in duration, or not responding to drugs).

Neuroimaging is recommended for coverage with headache when a red flag* is present.

*The following represent red flag conditions for underlying abnormality with headache:

- new onset or change in headache in patients who are aged over 50
- thunderclap headache: rapid time to peak headache intensity (seconds to 5 min)
- focal neurologic symptoms (e.g. limb weakness)
- non-focal neurological symptoms (e.g. altered mental status)
- abnormal neurological examination
- headache that changes with posture
- headache wakening the patient up
- headache precipitated by physical exertion or Valsalva maneuver (e.g. coughing, laughing, straining)
- patients with risk factors for cerebral venous sinus thrombosis
- jaw claudication
- nuchal rigidity
- new onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
- new onset headache in a patient with a history of cancer
- headache with a history of dizziness, lack of coordination, numbness or tingling
- cluster headache, paroxysmal hemicrania or Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA)

➤ **Topic: Attention Deficit Hyperactivity Disorder**

Discussion: Little reviewed the expert comment disposition from the meeting materials.

Westbrook said that for her, this draft is preferable to the older one. Her initial concern was the cookie cutter approach allowing a parent training program as the only behavioral therapy treatment option for children under six, as well as concerns related to children who have comorbid diagnoses. She said that behavioral health is different than medicine as there is not always one approach to something.

Westbrook said she has received additional comments from interested parties saying that cognitive therapy has some benefits, but children do better with family therapy. In addition, adolescents and adults do better with a more cognitive approach. She also received literature showing neurofeedback is helpful for both children and adults as well as mindfulness training, compound herbs and computer programs that train working memory. Some say 20-30% of adolescents will not benefit from medication or behavioral therapy. A clinician needs to have other options for this population.

Livingston reviewed the changes to the coverage guidance box and clarified that the additions shown in green are based on expert opinion and internal subcommittee recommendations, and not necessarily on the trusted evidence sources. Several changes were made based on subcommittee and expert input:

Addition of “diagnosed”

The draft guidance in the meeting materials includes the word “diagnosed,” in order to indicate that an official diagnosis needs to be made, although diagnostic criteria fall outside the scope of this coverage guidance. There was no discussion.

Provider-teacher consultations

For children under age 6, the recommendation for coverage of provider-teacher consultations has been changed from a strong recommendation to a weak recommendation for coverage, as the removal of the restriction of such consultations to children of low socio-economic status is not supported by the evidence sources. However, the subcommittee felt it was important not to restrict this based on socio-economic status.

As requested at the February meeting, Livingston researched the question regarding funding for school interventions versus medical environment. School and medical interventions are from different funding sources and have different goals. The goal with medical treatment is to optimize, while

the educational system's goal is to improve function in school to a certain level. Funding from Medicaid doesn't go towards the school interventions. Thus only the provider-teacher consultation is within scope of the coverage guidance document.

After discussion the subcommittee agreed that covering a provider consultation with a teacher was an appropriate way for the medical system to coordinate with evidence-based educational techniques performed by school staff. Thus they chose to keep the recommendation even though it is not directly supported by the evidence, except for the evidence for children under age 6 who have low socioeconomic status. The recommendation will be modified in the GRADE table.

Other treatments for children under 6

In addition, the new draft contains language recommending coverage for other behavioral and psychosocial treatments for children under the age of six. Staff has no current evidence supporting this coverage but it was added for discussion.

The subcommittee discussed the lack of evidence supporting this recommendation. There was a discussion about maintaining fidelity to the evidence versus supporting individualized treatment. Westbrook said that she had some evidence supporting this recommendation. After discussion the subcommittee decided to ask Little to review Westbrook's evidence related to the use of 'behavior therapy alone in children under 6 and to perform a brief focused search of the literature on this topic and report back at the next meeting.

Comorbidities

In addition, a footnote specifying that treatment with comorbid conditions may require different or additional treatments appears in the draft version in the meeting materials, per subcommittee request at the February meeting. There was no discussion.

Actions:

- 1) Staff to update the public comment disposition, GRADE table and box language, finalizing the including the comorbidity footnote and including the term "diagnosed" as shown in the meeting materials.
- 2) Review articles provided by Westbrook and do a brief focused literature review to answer the questions about behavioral therapies under the age of six
- 3) Bring back draft coverage guidance to next EbGS meeting for review and possible approval

➤ Topic: Prenatal Genetic Testing

Discussion: Livingston introduced the draft coverage guidance on prenatal genetic testing. Livingston noted that for this topic, the three high-quality prenatal guidelines identified addressed some but not all of the topics covered in the GRADE table. For the remainder of the tests, they came from 24 guidelines of unknown quality. In many cases, the subcommittee will be operating in with very limited evidence. Even though evidence may be insufficient to demonstrate the most likely outcomes for specific tests, many of these tests share similar characteristics in that they inform reproductive decision making for current and future pregnancies, with the potential to alter pregnancy management or immediate newborn care, depending on the condition. Livingston presented each type of testing with the evidence or expert input which informs the recommendation. Cori Feist, a genetic counselor at OHSU, Dr. Suzanne Lubarsky and Dr. Brian Shaffer provided clinical expertise on this topic. However, only Feist was able to attend the meeting.

In the review of the row on CVS and amniocentesis, the subcommittee discussed whether to recommend coverage for the test based on maternal request. They decided to recommend it, based on expert input, despite the risk of pregnancy loss. But because of this risk, the draft shows pre-test genetic counseling as strongly recommended. After discussion the subcommittee decided to make the recommendation for genetic counseling a “recommendation for coverage,” to clarify that the counseling should be covered as well as the test, and to make it a weak recommendation.

The committee decided to make no recommendation at all for aneuploidy testing with QF-PCR, as this test is not available in the United States.

In Array CGH testing when the karyotype is normal and there is a structural anomaly on ultrasound, the subcommittee decided to remove the recommendation for genetic counseling, as counseling would already have occurred before the CVS/amniocentesis. For Array CGH with stillbirth at >20 weeks gestation, the subcommittee decided to strike the recommendation, as none of the evidence reviewed supports its use in improving future pregnancy outcomes.

Livingston said that cell free fetal DNA testing is a new test (only available in the last 6 months), but one with high sensitivity and specificity. However, it is not recommended for coverage because serum screens are much less expensive. Feist said that it would cut down on CVS and amniocentesis due to false positives with the serum screening, but any positives would still need to be confirmed with invasive testing. Saha noted that despite the reduction in amniocentesis, the test won't reduce cost even if it reduces amniocentesis because it costs as much as amniocentesis and would require a follow-up amniocentesis if positive.

For thrombophilia screening, the subcommittee discussed how the risk of treating after a positive test compares with no test or treatment and it was clarified that the risk is unknown based on a lack of data. After discussion the subcommittee decided to change the recommendation to clarify that the recommendation applies to women with a history of recurrent pregnancy loss and that screening for thrombophilia was not recommended.

During this discussion, the subcommittee requested that staff revise the HERC Coverage Guidance Development Framework to include a path on the side for treatments of unknown effectiveness to allow for treatments where the risk versus the alternative treatment is unknown.

For spinal muscular atrophy, Chan asked whether high risk patients are well-defined. Feist said that this condition is the most common autosomal recessive disorder in humans regardless of ethnicity (1 in 35 people is a carrier), but ethnic groups other than Caucasian and those with a family history are at higher risk. Seventy percent of children with the disorder pass away before their tenth birthday. However, there is no evidence supporting the test and professional guidelines have conflicting recommendations. After discussion the subcommittee agreed to change the language to “screening for spinal muscular atrophy is recommended for coverage once in a lifetime only with pretest genetic counseling (weak recommendation).”

For the diseases specific to the Ashkenazi Jewish population, the subcommittee debated whether to cover four or eight tests. Feist said that the additional four tests are for conditions that are slightly less common. One has a treatment, but the others are extremely debilitating. Cost varies widely depending on the lab. After discussion the subcommittee decided to leave coverage for only four conditions (Tay-Sachs disease, Canavan disease, cystic fibrosis and familial dysautonomia).

The subcommittee discussed the applicability of the HERC Coverage Guidance Development Framework to diagnostic procedures.

Garside and Saboe needed to leave the meeting due to other commitments so the subcommittee tabled discussions as no quorum was present after their departure.

Actions: The subcommittee will continue discussion of this topic at the June meeting.

➤ **Public Comment:**

No members of the public offered additional public comment.

➤ **Issues for next meeting:**

Livingston asked the remaining subcommittee members whether the subcommittee would like experts for the topic of botulinum toxin type A for prophylaxis of chronic migraine and tension headaches, which will be the next topic for the subcommittee's consideration. Subcommittee members agreed that they did not need an expert if the evidence is sufficient. Little said there is adequate evidence to make a coverage recommendation included within the 2012 MED report.

➤ **Next meeting:**

June 6, 2013, 2 – 5 p.m. at Meridian Park Hospital, room 117B.

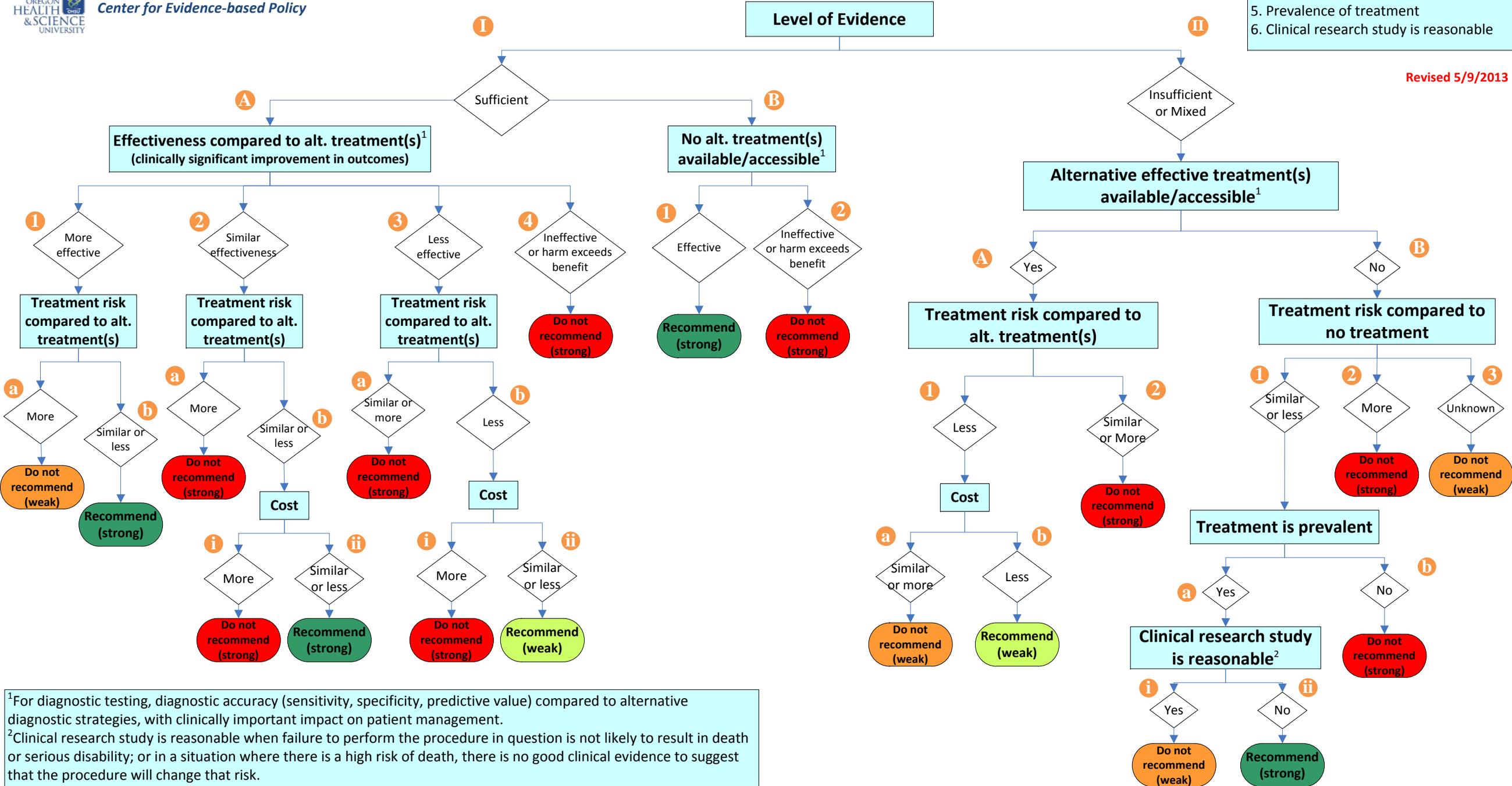
DRAFT

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

Revised 5/9/2013



HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgement. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

Coverage Guidances Review

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE: PRENATAL GENETIC TESTING

DRAFT for EbGS Meeting Materials 6/6/2013

HERC COVERAGE GUIDANCE

The following are recommended for coverage (*weak recommendation*):

- Pretest genetic counseling prior to CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening.
- Validated questionnaire to assess genetic risk in all pregnant women
- Screening high risk ethnic groups for hemoglobinopathies
- Screening for aneuploidy with any of the four screening strategies (integrated, serum integrated, stepwise sequential, and contingency)
- Ultrasound for structural anomalies between 18 and 20 weeks gestation
- CVS and amniocentesis for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, positive family history, elevated risk of neural tube defect, or maternal request
- Array CGH when major fetal congenital anomalies apparent on imaging, and karyotype is normal
- FISH testing only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
- Screening for Tay-Sachs carrier status in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
- Screening for cystic fibrosis carrier status once in a lifetime
- Screening for fragile X status in patients with a family history of unexplained mental retardation or a history of fragile X mental retardation, premature ovarian failure, adult onset ataxia, or unexplained autism through the pregnant woman's maternal line
- Screening for spinal muscular atrophy once in a lifetime
- Screening those with Ashkenazi Jewish heritage for Canavan disease and familial dysautonomia
- Expanded carrier screening only for those genetic conditions identified above

The following are not recommended for coverage (*weak recommendation*):

- Serum triple screen
- ~~Aneuploidy testing with QF-PCR~~
- Cell free fetal DNA testing
- Screening for thrombophilia in general population or for recurrent pregnancy loss
- Expanded carrier screening for conditions without explicit recommendations for coverage

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

Little, A., Vandegriff, S., Zoller, E., Pettinari, C., Mayer, M., Kriz, H., & King, V. (2013). *Prenatal genetic testing: Evidence and guideline summary of select tests and conditions* [Produced for the Medicaid Evidence-based Decisions (MED) Project]. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

Key Sources Cited in MED Report:

Akkerman, D., Cleland, L., Croft, G., Eskuchen, K., Heim, C., Levine, A., et al. (2012). *Routine prenatal care*. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI). Retrieved August 2, 2012, from <https://www.icsi.org/asset/13n9y4/Prenatal-Interactive0712.pdf>

Department of Veterans Affairs, & Department of Defense. (2009). *VA/DoD clinical practice guideline for pregnancy management*. Washington, DC: Department of Veterans Affairs, Department of Defense. Retrieved June 19, 2012, from <http://www.healthquality.va.gov/pregnancy.asp>

National Collaborating Centre for Women's and Children's Health, & National Institute for Health and Clinical Excellence (NICE). (2008). *Antenatal care: Routine care for the healthy pregnant woman*. London: RCOG Press. Retrieved June 19, 2012, from <http://www.nice.org.uk/guidance/CG62>

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Genetic testing detects alterations in DNA or chromosomes. Human genetic testing requires laboratory analyses of DNA, which is isolated from biologic samples, including cells, blood, or amniotic fluid. Tests for more than 1,300 genetic conditions are available. Genetic tests can be used to diagnose, predict risk for a future disease, inform reproductive decision-making, and manage patient care. There are eight categories of genetic testing: diagnostic, predictive, pharmacogenomic, prenatal, carrier, preimplantation, newborn, and research testing. This guidance document will focus only on recommendations for prenatal, carrier and diagnostic genetic testing. Prenatal testing is used to identify a fetus's genes or chromosomes before birth and is offered during pregnancy based on the risk that the baby will have a genetic or chromosomal disorder. Carrier testing is used to identify people who carry one copy of a gene mutation, which can cause a genetic disorder if two copies are present. Carrier testing is primarily offered to those with a family history of a specific genetic disorder and high-risk ethnic groups. Diagnostic testing is used to identify a specific genetic or chromosomal condition, and to confirm a diagnosis when a particular condition is suspected.

Evidence Review

General Prenatal Testing

A search of guideline databases (MED core sources plus the American College of Medical Genetics and the Canadian College of Medical Geneticists) was conducted from 2008 to present and identified 28 guidelines, three of which addressed general prenatal care [NICE (2008), VA/DoD (2009), and ICSI (Akkerman [ICSI] 2012)]. All three were rated good quality and provided detailed guidance on general prenatal care, with specific recommendations related to genetic testing. All three recommend screening measures and testing indications for aneuploidy screening, general risk assessment and screening options for hemoglobinopathies, cystic fibrosis, and structural abnormalities. One guideline addresses screening for Tay-Sachs disease. Recommendations from all three guidelines are consistent with a few exceptions:

- Ultrasound screening for structural anomalies is recommended only by NICE (optional for ICSI and VA/DoD); and
- Method of aneuploidy screening is specified only by NICE, which recommends the combined test in the first trimester as the most desirable strategy. The other two guidelines do not recommend one strategy for testing over another.
- NICE does not recommend carrier testing for cystic fibrosis

Prenatal genetic testing recommendations are summarized and compared in the table below:

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
Genetic risk assessment	Validated questionnaire	Validated questionnaire	Validated questionnaire
Hemoglobinopathies	Screen all high-risk ethnic groups ¹ , complete blood count test, hemoglobin electrophoresis test.	Screen all high-risk ethnic groups, complete blood count test, hemoglobin electrophoresis test.	Screen all high-risk ethnic groups, complete blood count test, hemoglobin electrophoresis test.
Cystic fibrosis	Addressed in separate guideline – testing not recommended	Carrier test/counseling	Carrier test/counseling
Tay-Sachs disease	-	-	Leukocyte hexosaminidase A test for high-risk ethnic groups
Aneuploidy screening	<p>First choice (for women who enter care in the first trimester): nuchal translucency (NT), beta-human chorionic gonadotropin (beta-hCG), and pregnancy-associated plasma protein A (PAPP-A) (11 weeks 0 days and 13 weeks 6 days);</p> <p>Second choice (for women who present later in the pregnancy): triple² or quadruple³ test</p>	<p>Any of the following, based on the woman's choice: First- or second-trimester serum marker assessment, first-trimester NT measurement, basic and comprehensive second-trimester ultrasound assessment, first-trimester chorionic villus sampling and second-trimester amniocentesis.</p> <p>If first trimester screening is elected: second-trimester serum AFP screening and/or US should be offered to screen for open neural tube</p>	Any of four screening strategies (integrated, serum integrated, stepwise sequential, and contingency) ⁴ .

¹ Women of African, Southeast Asian (excluding Japanese and Korean) or Mediterranean descent

² Serum AFP, estriol and beta-hCG

³ Serum AFP, estriol, beta-hCG and dimeric inhibin A

⁴ See below for description of these screening strategies

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
	(15 weeks 0 days and 20 weeks 0 days).	defects. For second trimester serum screening: Quad Marker Screen should be used rather than the Triple Marker Screen.	
Structural abnormality screen	Between 18 weeks 0 days and 20 weeks 6 days	Optional - only as needed	Optional 18-20 weeks
Chorionic Villus Sampling (CVS) or Amniocentesis	Provide information at first visit Offer if positive aneuploidy screening (details not provided) Offer if both parents are sickle cell or thalassemia carriers	Maternal request Offer CVS in first trimester if: <ul style="list-style-type: none"> • Age over 34 • Abnormal first trimester screen (risk estimate similar to that of 35 year old woman [1/270]) • Fetal structural anomalies • Positive family history for metabolic/genetic disorder Offer amniocentesis if: <ul style="list-style-type: none"> • Abnormal first or second trimester screen (risk estimate similar to that of 35 year old woman [1/270]) • Fetal ultrasound anomalies • Positive family history for metabolic/genetic disorder • Elevated risk of open neural tube defect 	Three different screening algorithms provided, with no recommendation for which to use Perform risk assessment using first trimester strategy (nuchal translucency, serum PAPP-A, patient age) and/or second trimester strategy (triple or quad screen) High, intermediate and low risk not specified, but examples given (1/50, 1/200) CVS or amniocentesis offered if screening suggests "high risk", depending on gestational age

Screening strategies as outlined in the ICSI guideline:

- Integrated screening: The patient is scanned for nuchal translucency determination and has a serum PAPP-A analysis performed between 10 and 13 weeks. The results of these tests are held, and the patient then has a quadruple screen test performed between 15 and 19 weeks. At that time, the results of all the studies, combined with risk assessment due to the patient's age, are used to present a single-risk figure. Patients at "high risk" are offered amniocentesis (Trisomy 21 detection rate = 94-96%). "High risk" is not defined, but qualified with the following language: "Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff."
- Serum integrated screening: A variation in which the first-trimester PAPP-A test result is combined with a second-trimester quad test to provide a single-risk figure is called a serum integrated screening. (Trisomy 21 detection rate = 85-88%).
- Stepwise sequential screening: The patient is scanned for nuchal translucency determination and has a serum PAPP-A analysis performed between 10 and 13 weeks. The results of these studies are combined with the patient's age-associated risk, and the patient is given a risk assessment for aneuploidy. The patient may choose at this time to undergo invasive testing (i.e., CVS), or a triple or quad screen at 15-19 weeks. If the patient has the second-trimester test, a new risk is assessed based on the results of her age and both the first- and second-trimester screening test results (Trisomy 21 detection rate = 95%). Those at "high risk" are offered amniocentesis. "High risk" is not defined, but qualified with the following language: "Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff."
- Contingency screening: The patient has the same first-trimester study described for the stepwise sequential test and is told the results. If the results are above an arbitrary cutoff, such as 1 in 50, she is offered CVS. If her results are below another arbitrary cutoff, such as 1 in 1,000, she is advised that no further testing is necessary. If the patient's risk falls between these two cutoffs, she is offered a quad screen after 15 weeks, and a new risk assessment is determined as in the stepwise sequential test (Trisomy 21 detection rate = 88-94%). Those at "high risk" are offered amniocentesis. "High risk" is not defined, but qualified with the following language: "Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff."

Genetic Counseling

The NICE guideline does not address women with a family history of a genetic disorder, or specify indications for genetic counseling. The ICSI guideline does not specify indications for genetic counseling with the exception of women with a family history of Fragile X disease or mental retardation. The VA/DoD guideline recommends that genetic counseling be provided to any woman identified as high risk, defined as advanced maternal age, personal or family history of genetic disorder or positive screening test result.

Specific Prenatal Tests or Testing Techniques

A search of clinical evidence sources and guideline databases (MED core sources plus the American College of Medical Genetics and the Canadian College of Medical Geneticists) was conducted from 2003 to present (2008 to present for guidelines). Twenty-four evidence reviews and 28 guidelines were identified, all of which addressed specific genetic tests with the exception of the three general prenatal guidelines discussed above. No quality assessment of the guidelines was done.

Fetal Aneuploidy

Prenatal diagnosis of aneuploidy is suggested by use of maternal screening tests, as reviewed above. All such tests have less than perfect sensitivity and require definitive fetal testing if abnormal. Definitive testing for aneuploidy has historically been an invasive procedure, accomplished by amniocentesis or chorionic villus sampling. However, recently, other methods to detect common aneuploidies have been developed. Four of these are outlined below.

Quantitative Fluorescent-Polymerase Chain Reaction (QF-PCR)

This is a PCR-based technique that consists of amplifying polymorphic markers located on the chromosomes of interest (generally, chromosomes 13, 18, 21, X or Y) to determine the number of copies of those chromosomes present per cell. The advantages of QF-PCR are that it requires a small sample (culture of amniocytes is not required), and the procedure can be automated, providing a rapid turnaround time at a lower cost than conventional cytogenetics. Moreover, diagnostic testing with QF-PCR eliminates the unexpected or incidental identification of rare chromosomal abnormalities of uncertain significance.

No evidence was identified that addressed this test. One guideline was identified, produced by collaboration of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) joined with the Prenatal Diagnosis Committee of the Canadian College of Medical Genetics in 2011. They state that “*QF-PCR is a reliable method to detect trisomies and should replace conventional cytogenetic*

analysis whenever prenatal testing is performed solely because of an increased risk of aneuploidy in chromosomes 13, 18, 21, X or Y.”

Microarray Testing

Microarray testing generally refers to array comparative genomic hybridization (array CGH), which uses a high resolution analysis of the genome to identify losses or duplications to the chromosome. These deletions and duplications are referred to as copy number variations (CNV). Conventional chromosome analysis using G-banding will detect chromosome anomalies such as trisomies 21, 18 and 13, and monosomy X, along with many structural rearrangements. However, it only detects anomalies to a resolution of 5-10 Mb (million base-pairs). Array CGH, on the other hand, is capable of detecting changes to a resolution of 1 kb (thousand base-pairs) which is smaller than the average gene, and customized arrays designed for prenatal diagnosis have been developed.

One of the challenges of the application of CGH microarrays in the clinical setting is determining whether a copy number imbalance is *de novo* and likely to be causative, or inherited and likely to be benign. Copy number variants (CNVs) are categorized into those that are likely to be ‘benign,’ those that are likely to be ‘pathogenic’ and those of ‘unknown clinical significance.’ Copy number variants that overlap critical regions of established microdeletion or microduplication syndromes are likely to be pathogenic, but there is a high incidence of CNVs in the normal population, making the significance of many CNVs uncertain. Although array CGH has higher resolution to detect these small chromosomal changes, it cannot detect balanced rearrangements such as transformations or inversions. Identifying CNVs of uncertain significance increases parental anxiety and makes genetic counseling more challenging.

For microarray testing, a systematic review found that array CGH detected 3.6% additional genomic imbalances when conventional karyotyping was normal, regardless of the reason for performing the study, and increased to 5.2% when the indication for performing the study was a structural malformation on ultrasound. Three guidelines were identified that address array CGH and make similar recommendations. None of the three recommend array CGH testing for pregnancies at low risk of chromosome abnormalities. All three recommend this technology when fetal structural abnormalities are identified on ultrasound or MRI, although one recommends that it be utilized only if conventional karyotyping is normal. All three also recommend genetic counseling for all patients utilizing the technology.

Fluorescent In Situ Hybridization (FISH) DNA Testing

This is a rapid technique that relies on fluorescent in situ hybridization (FISH) that provides results in one to two days, in which fluorescently labeled DNA probes are

bound to fetal cell DNA in a highly selective manner, allowing detection of changes in the number of specific chromosomes by detecting the fluorescence. To detect the most common disorders involving chromosome number, fluorescent probes are used that bind to chromosomes 13, 18, 21, X, and Y. However, this technique fails to detect many other potentially harmful changes in chromosomes that can be detected by conventional karyotyping, such as certain rearrangements of segments of chromosomes.

One TA was identified that addressed this topic. It included three large studies that compared results obtained with FISH with those obtained with conventional karyotyping. Results suggest that FISH is a highly accurate test for detection of most, but not all, potentially harmful chromosomal abnormalities, with sensitivity and specificity for detection of the targeted abnormalities exceeded 99.5%. However, it is unable to detect 7% to 11% of potentially harmful chromosomal disorders that can be detected by karyotyping.

Cell Free Fetal DNA Testing

Fetal DNA circulates in maternal blood during pregnancy, making up approximately 10% of all circulating DNA. Recently, cell free DNA testing has been used to identify common aneuploidies. These tests utilize maternal blood, from which fetal DNA can be isolated as early as ten weeks gestation. Repeated parallel sequencing can then detect an excess of the chromosome of interest of fetal origin, indicating the specific aneuploidy.

No evidence was identified. One guideline recommends that cell free DNA testing be offered to patients at increased risk of aneuploidy⁵. They recommend that it NOT be a part of routine prenatal laboratory measurements or be offered to low risk women.

Tay-Sachs Disease

Tay-Sachs disease is an autosomal recessive lysosomal storage disease caused by a deficient activity of the enzyme hexosaminidase A (Hex A). It occurs in 1 in 2500 children of Ashkenazi Jewish parents, and is most common among people who are Ashkenazi Jewish, French-Canadian, or Cajun. Hex A activity can be measured in serum, white blood cells, or fetal trophoblastic cells, and is used as the initial screening test for TSD mutation carriers. However, in some cases, the enzyme test may not be diagnostic, and DNA analysis may be necessary to clarify ambiguous enzyme test results or to diagnose variant forms of the disease.

One review that included four studies and a retrospective analysis found that hexoaminidase A testing is accurate and impacts both pre and post-conception

⁵ Maternal age \geq 35, suggestive US findings, history of prior trisomy pregnancy, positive aneuploidy screen or parental balanced robertsonian translocation with increased risk for fetal trisomy 13 or 21

reproductive decision making. The review concludes that the evidence is sufficient to support the use of screening by Hex A enzyme testing individuals at high risk (Ashkenazi Jewish, French-Canadian or with positive family history) or partners of known carriers. It is also sufficient to support additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A. The one guideline identified recommends that Hex A screening be offered to all pregnant Jewish patients if they or their partners have not yet been tested.

Cystic Fibrosis

Cystic Fibrosis is an autosomal recessive disease of the exocrine glands that is characterized by early onset of severe intestinal malabsorption, failure to thrive and recurrent chest infections and pneumonia which, if untreated, leads to death from malnutrition and respiratory failure in infancy or early childhood. The identification of the gene responsible for CF, *CFTR*, and its major mutations, allow for the identification of couples at risk who can be offered genetic counseling and prenatal CF diagnosis, and who can use the information to inform reproductive decision-making. Since heterozygotes are asymptomatic, carrier status assumes clinical significance only in the context of reproduction.

A review of 10 population-based studies found carrier testing was 80% to 96% sensitive in Caucasians and 58% to 76% sensitive in Hispanics. Uptake rates for testing ranged from 68% to 95%. The evidence was sufficient to support the use of CF carrier screening if results will be used to guide decisions regarding childbearing or need for fetal diagnosis. A second review reported analytic sensitivity of 97.9% and analytic specificity of 99.4%, but clinical sensitivity of only 75%. Uptake rates in this review were reported as 85% to 100%, and of the affected fetuses identified, 83% were terminated. Four guidelines were identified, three of them addressing general prenatal care and offering differing recommendations. Two recommend that CF carrier screening be offered to all couples who desire it and have not been previously screened, while the third does not recommend screening. The one guideline that addressed CF carrier screening outside the context of general prenatal care recommends carrier testing in individuals and their partners with a positive family history, and prenatal diagnosis for pregnancies at 25% or greater risk of CF, and those with an echogenic bowel identified in the fetus.

Fragile X Syndrome

Fragile X Syndrome is the most common inherited cause of mental retardation, and results from a dynamic mutation (those that can change as they are passed down to future generations). In normal individuals there are six to 50 repeats of the CGG sequence of DNA at the Fragile X site. When the number of repeats ranges between 50 and 200, this is known as a premutation (PM); more than 200 repeats is considered a

full mutation (FM). Full mutations inactivate the gene resulting in the Fragile X phenotype in all males (who only have one copy of the gene) and a proportion of females (all will be carriers, some will have the phenotype). A female with a PM or a FM may pass on a larger mutation than her own, resulting in offspring affected by Fragile X syndrome. Meanwhile, men with a PM may pass this onto their daughters, who will be of normal intellect, but may pass a larger mutation onto their offspring. The larger the size of the premutation repeat, the more likely is the expansion to a full mutation.

A systematic review that compared antenatal screening of low risk versus high risk women identified no studies, while a health technology assessment that compared different screening strategies for Fragile X syndrome found that population-based prenatal screening is more efficacious but significantly more costly than active cascade screening⁶, with the incremental cost per Fragile X birth avoided being £8494 for active cascade screening and £284,779 for population-based screening. Three guidelines address testing for Fragile X and offer generally consistent recommendations. These include genetic counseling of all testing recipients, carrier screening of women with a positive personal or family history of fragile X-rated disorders, unexplained mental retardation or premature ovarian failure, and prenatal fetal DNA testing for known carriers.

Heritable Thrombophilia

Pregnancy is associated with an increased risk of venous thromboembolism, as are inherited thrombophilias. However, it is controversial whether there is an association between inherited thrombophilias and adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption. This possible association has resulted in increased screening for thrombophilias in pregnancy, although there has been no confirmation of treatment benefits.

For heritable thrombophilia, one systematic review resulted in a recommendation to not screen for heritable thrombophilia in any group. One guideline was identified that addresses inherited thrombophilias in pregnancy. Regarding screening, it recommends against testing in women with recurrent fetal loss or placental abruption, and finds insufficient evidence to support testing in women with previous preeclampsia or intrauterine growth restriction. For women diagnosed with hereditary thrombophilia and/or with a history of thromboembolism, the guideline provides specific recommendations for which tests to perform, and for antepartum and postpartum management.

⁶ Testing relatives of Fragile X patients to determine carrier status

Fetal Skeletal Dysplasia

Skeletal dysplasias may present in the prenatal period when demonstrated by abnormalities on ultrasound. Differentiating these disorders in the prenatal period can be useful to distinguish known lethal disorders from nonlethal disorders and to assist with determining post-delivery management plans. One guideline was identified that provides specific recommendations for management based on abnormal findings of a second trimester ultrasound. Those recommendations include a determination of lethality based on ultrasound measurements, and molecular testing of pregnancies identified as at-risk for skeletal dysplasias.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness. The incidence of SMA is approximately 1 in 10,000 live births, and it is reported to be the leading genetic cause of infant death, although milder forms allow survival into adulthood. Two guidelines were identified, with conflicting recommendations. One did not recommend screening for SMA in the general population, but did recommend carrier screening for those with a family history of SMA-like disease. The other recommends that carrier testing be offered to all couples.

Ethnicities with Elevated Genetic Risk

For ethnicities at increased genetic risk, two guidelines were identified with conflicting recommendations for screening those of Ashkenazi Jewish descent. Both recommend carrier screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia. One also recommends screening for Fanconi anemia, Bloom syndrome, Mucopolysaccharidosis IV, Niemann-Pick type A and Gaucher disease type I, while the other only recommends that patient education materials be made available to patients concerning these conditions. Both groups also recommend carrier screening for Tay Sachs disease for individuals of French Canadian and Cajun origin.

Genetic Counseling

All three guidelines pertaining to microarray testing recommend that it be accompanied by genetic counseling. Guidelines addressing other specific genetic tests recommend genetic counseling be provided in the following situations: a positive cell free fetal DNA testing result, any cystic fibrosis carrier, women with risk factors for Fragile X or who request testing for Fragile X and women with a family history of, or who request testing for, spinal muscular atrophy.

Evidence Summary

Evidence-based guidelines for routine prenatal care are generally consistent regarding their recommendations related to genetic testing, recommending aneuploidy screening

and screening options for hemoglobinopathies, cystic fibrosis, and structural abnormalities. Recommendations on specific tests were generally not based on trusted sources due to lack of availability of evidence and are derived from guidelines of variable quality.

There are four options available for aneuploidy testing in addition to the traditional method of karyotyping, which requires an invasive procedure (amniocentesis or chorionic villus sampling) and amniocyte culture. Three of the four do not require the culture of amniocytes, allowing a more rapid turnaround time, but at the expense of a less accurate or complete diagnosis. They include QF-PCR, FISH testing and cell free fetal DNA testing. No evidence was identified for QF-PCR or cell free DNA testing, while evidence for FISH suggests that it is a highly accurate test for detection of most potentially harmful chromosomal abnormalities, although it is unable to detect 7% to 11% of chromosomal disorders that can be detected by karyotyping.

The fourth method, array CGH testing, is limited by difficulty determining whether a copy number imbalance is likely to be causative or benign, as well as the inability to detect balanced rearrangements. Evidence suggests that array CGH detects approximately 5% additional genomic imbalances when conventional karyotyping is normal, if the indication for performing the study is a structural malformation on ultrasound. None of the three identified guidelines recommend array CGH testing for pregnancies at low risk of chromosome abnormalities, but all recommend it when fetal structural abnormalities are identified.

For Tay-Sachs disease, the evidence is sufficient to support the use of screening by Hex A enzyme testing for individuals at high risk (Ashkenazi Jewish, French-Canadian or with positive family history) or partners of known carriers. It is also sufficient to support additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A.

For cystic fibrosis, the evidence is sufficient to support the use of CF carrier screening if results will be used to inform decisions regarding childbearing or need for fetal diagnosis.

For Fragile X Syndrome, three guidelines recommend carrier screening of women with a positive personal or family history of Fragile X-rated disorders, unexplained mental retardation or premature ovarian failure, and prenatal fetal DNA testing for known carriers.

For heritable thrombophilia, evidence supports and one guideline recommends not screening for heritable thrombophilia in any group.

For fetal skeletal dysplasia, one guideline recommends determining lethality based on ultrasound measurements and molecular testing of at-risk pregnancies.

For spinal muscular atrophy, two guidelines had conflicting recommendations, with one recommending carrier screening to all couples and the other recommending only for those with a family history of SMA-like disease.

For ethnicities at increased genetic risk, two guidelines recommend screening those of Ashkenazi Jewish descent for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia, but disagree about screening for four additional conditions.

DRAFT

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
Use a validated questionnaire to assess genetic risk in all pregnant women	Likely beneficial without known risks	Low	Limited	Limited variability		Administration of a validated questionnaire to assess genetic risk is recommended for coverage <i>(weak recommendation)</i>
Screen high-risk ethnic groups for hemoglobinopathies	Likely beneficial, minimal risks	High	Limited	Limited variability		Screening high risk ethnic groups for hemoglobinopathies is recommended for coverage <i>(weak recommendation)</i>
Aneuploidy screening in first or second trimester	Likely beneficial, minimal risks	Moderate	Moderate	Moderate variability		Screening for aneuploidy with any of the four screening strategies (integrated, serum integrated, stepwise sequential, and contingency) is recommended for coverage <i>(weak recommendation)</i> Serum triple screen is not recommended for coverage

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
						<i>(weak recommendation)</i>
Perform an US for structural anomaly screen at 18-20 weeks	Possibly beneficial, minimal risks	Low	Moderate	Limited variability		Ultrasound for structural anomalies between 18-20 weeks gestation is recommended for coverage <i>(weak recommendation)</i>
Offer CVS or amnio for + aneuploidy screen, maternal age > 34, fetal structural anomalies, + FH, elevated risk of neural tube defect or maternal request	Mixed – Moderate benefit depending on patient preferences, small risk (pregnancy loss 1/300-500)	Mixed	High	High variability	Very few low risk women choose to have CVS/amnio. If family history, would be very appropriate.	CVS and amniocentesis are recommended for coverage for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, positive family history, elevated risk of neural tube defect, or maternal request <i>(weak recommendation)</i> Genetic counseling is recommended for coverage prior to CVS/amniocentesis <i>(weak recommendation)</i>
Aneuploidy testing with QF-PCR	Similar risk to karyotyping, may be more beneficial when rapid turnaround is required	None	Moderate	High variability	Can't get it done in US. FISH should be used instead.	<i>Test not available in the US – no recommendation made</i>
Array CGH testing when karyotype normal and structural anomaly on US	Similar risk to karyotyping, similar benefits (detection of more chromosomal anomalies, but also more anomalies of no clinical significance,	Low	Moderate	Limited variability (because anomalies already identified)	Karyotyping would be preferred. Could be second tier test. Identified another 2.5-6% of important abnormalities. Doubles impact of karyotype, would miss large number of clinically significant chromosomal	Recommended for coverage when major fetal congenital anomalies apparent on imaging and karyotype is normal <i>(weak recommendation)</i>

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
	resulting in increased maternal anxiety				abnormalities. 1-3% clinically questionable and much higher than expected. If fetal demise, often have difficulty with culture failure, and then wouldn't have an answer. Almost the same cost as karyotyping. No evidence for use in stillbirth, chromosomal assessment is considered standard, but array versus standard karyotype as standard unknown.	
Aneuploidy testing with FISH	Similar risk to karyotyping, may be more beneficial when rapid turnaround is required	Moderate	High	High variability (because use for pregnancy decision making only)	FISH is important if rapid turnaround is necessary (for example 23w4d gestation with newly identified anomalies). Would also use on stillbirth or fetal demise. Earlier than 22w4d should not be offered FISH. It is very expensive.	Karyotyping is first line test. If a rapid turnaround (i.e. at 22w4d or beyond) is required for reproductive decision-making, FISH is recommended for coverage (<i>weak recommendation</i>)
Cell free fetal DNA testing	High level of accuracy (98% detection rate with false positive < 0.5%). Less risk than karyotyping but less information	None	High	Moderate variability (many women would choose a noninvasive highly accurate test)	If have structural abnormality on US, should go for invasive testing. For screening, very expensive, has 1% false positive and 1% false negative rate.	Cell free fetal DNA testing is not recommended for coverage (<i>weak recommendation</i>)

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
	provided (current tests only identify trisomy 13, 18 and 21)				Decreases the number of amioncenteses significantly, save pregnancy losses. If cost were significantly decreased, would likely replace serum screening.	
Screening for Tay-Sachs carrier status using Hex A in high risk populations ⁷	Benefits exceed harms	Moderate	Low	Limited variability (most would choose to terminate)	If positive, should reflex to mutation analysis, could be a pseudo-deficiency (maternal blood)	Screening for Tay-Sachs carrier status in high risk populations is recommended for coverage. First step is Hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A <i>(weak recommendation)</i>
Screening for CF carrier status	Potential benefit, minimal harm	Moderate	Moderate	Moderate variability	Limited variability (majority would choose to terminate or obtain fetal diagnosis). Would change 3 rd trimester management, reproductive changes, change delivery location. Only one should be covered ever – often get duplicates. Only once per lifetime.	Screening for cystic fibrosis status is recommended for coverage once in a lifetime <i>(weak recommendation)</i>
Screening for fragile X carrier status	Small benefit, depending on values of parents,	Low	Moderate	Moderate variability	Patients with a family history of unexplained mental retardation or a	Screening for fragile X carrier status is recommended for coverage in patients with a

⁷ Ashkenazi Jewish, French Canadian and Cajun

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
in women with +FH or risk factors ⁸	minimal harm				history of fragile X mental retardation premature ovarian failure, adult onset ataxia, unexplained autism. Reproductive decision making, can change recommendations on when to get pregnant if has premature ovarian failure, carriers learn about ataxia	family history of unexplained mental retardation or a history of fragile X mental retardation, premature ovarian failure, adult onset ataxia, or unexplained autism through the pregnant woman's maternal line (<i>weak recommendation</i>)
Screening for thrombophilia	No definite benefit, possible harm if prophylactic treatment undertaken (bleeding risks from anticoagulation)	Low	Moderate (if treatment undertaken)	Limited	Experts recommend for those with fetal loss after 10 weeks with placental ischemia and thrombosis (placental pathology looked at). No studies.	Screening for thrombophilia is not recommended for coverage for recurrent pregnancy loss <u>or in the general population</u> (<i>weak recommendation</i>)
Fetal genetic analysis of fetuses at risk for fetal skeletal dysplasia based on US	Mixed – Moderate benefit depending on patient preferences, small risk	Low	Moderate (cascade of testing)	Moderate variability	Can offer recurrence risk, survival possibilities, reproductive decision making. Consider removing this from coverage guidance altogether, non-standard prenatal genetic testing, it is rare with specific cascade of testing based on the type of findings on ultrasound.	<i>No recommendation made</i>

⁸ Personal or family history of fragile X tremor/ataxia syndrome, unexplained mental retardation, autism or premature ovarian failure (before age 40)

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
Spinal muscular atrophy carrier screening	Small benefit, depending on values of parents, minimal harm	None	Low	Moderate variability	American College of Medical Genetics recommends for it. ACOG recommends against it. Too difficult to counsel providers and pre and post test. Like fragile X. 5% of time can't get an answer with carrier screening. There are 4 clinical phenotypes, most common is the most severe. Grassroots efforts to screen for SMA. Pushing national screening from prepregnancy couples, esp in ashekanzi. It would change reproductive decision making, and would have polyhydramnios and breech.	Screening for spinal muscular atrophy is recommended for coverage once in a lifetime (<i>weak recommendation</i>)
Screening of Ashkenazi Jewish population for specific genetic diseases	Likely beneficial, minimal risks	Low	Moderate	Moderate variability	Conflicting recommendations on number of conditions to screen for. ACOG recommends 4 and ACMG recommends 8 tests.	Screening is recommended for coverage for those of Ashkenazi Jewish heritage for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia (<i>weak recommendation</i>)
Expanded carrier screening	Components likely beneficial, however, there is a risk of cascade testing, clinically	None	Moderate. There is a cascade of testing. However,	High variability	This incorporates screening for multiple carrier states, and as long as the clinician can select the specific	Coverage is recommended for expanded carrier screening only for those genetic conditions previously identified with enough evidence or

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
	unimportant results		compared to individual diagnostic tests, this type of testing is much less expensive		diseases screened for, is more cost effective. Would include Tay-Sachs, CF and others for a cost that is less than carrier screening for just one of these tests. However, if unlimited, 40% of people could test positive for something (e.g. could be sensitive to bright light, prenatal testing for male infertility)	<p>guidelines to support a weak recommendation for coverage (<i>weak recommendation</i>)</p> <p>Coverage is not recommended for an unlimited variety of tests offered as part of expanded carrier screening (<i>weak recommendation</i>)</p>
Genetic counseling	Beneficial in greater understanding of risks and benefits	Moderate	Cost of appointment may be balanced by optimizing appropriate test utilization	Low variability (most women would choose to see a genetic counselor)	Experts felt genetic counseling may improve appropriate ordering of tests. For spinal muscular atrophy screening, there is disagreement between genetic counseling guidelines and MFM guidelines.	Pretest genetic counseling is recommended for coverage prior to CVS, amniocentesis, Fragile X, microarray, and spinal muscular atrophy screening (<i>weak recommendation</i>)

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

There were no quality measures pertaining to prenatal genetic testing identified when searching the [National Quality Measures Clearinghouse](#).

COMMITTEE DELIBERATIONS –EBGS

COMMITTEE DELIBERATIONS – VBBS

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
V18.4	Family history of intellectual disabilities
V18.9	Family history of genetic disease carrier
V26.31	Testing of female for genetic disease carrier status
V26.32	Other genetic testing of female
V26.33	Genetic counseling
V26.34	Testing of male for genetic disease carrier status
V26.35	Encounter for testing of male partner of female with recurrent pregnancy loss
V26.39	Other genetic testing of male
V28.0	Antenatal screening for chromosomal anomalies by amniocentesis
V28.1	Antenatal screening for raised alpha-fetoprotein levels in amniotic fluid
V28.2	Other antenatal screening based on amniocentesis
V28.3	Encounter for routine screening for malformation using ultrasonics
V28.89	Other specified antenatal screening
V28.9	Unspecified antenatal screening
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81200	<i>ASPA (aspartoacylase)</i> (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81205	<i>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)</i> (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	<i>BLM (Bloom syndrome, RecQ helicase-like)</i> (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant)
81220	<i>CFTR (cystic fibrosis transmembrane conductance regulator)</i> (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	known familial variants
81222	duplication/deletion variants
81223	full gene sequence
81224	intron 8 poly-t analysis (eg, male infertility)
81225	<i>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	<i>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	<i>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228	Cytrogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	interrogation of genomic regions for copy number and single nucleotide

CODES	DESCRIPTION
	polymorphism (SNP) variants for chromosomal abnormalities
81240	<i>F2 (prothrombin, coagulation factor II)</i> (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	<i>F5 (coagulation Factor V)</i> (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	<i>FANCC (Fanconi anemia, complementation group C)</i> (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	<i>FMR1 (Fragile X mental retardation 1)</i> (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	characterization of alleles (eg, expanded size and methylation status)
81250	<i>G6PC (glucose-6-phosphatase, catalytic subunit)</i> (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	<i>GBA (glucosidase, beta, acid)</i> (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	<i>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)</i> (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	known familial variants
81254	<i>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)</i> (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	<i>HEXA (hexosaminidase A [alpha polypeptide])</i> (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	<i>HFE (hemochromatosis)</i> (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	<i>HBA1/HBA2 (alpha globin 1 and alphaglobin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81260	<i>IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)</i> (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81280	Long QT syndrome gene analyses (eg, <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> , <i>KCNJ2</i> , <i>CACNA1C</i> , <i>CAV3</i> , <i>SCN4B</i> , <i>AKAP</i> , <i>SNTA1</i> , and <i>ANK2</i>); full sequence analysis
81281	known familial sequence variant
81282	duplication/deletion variants
81290	<i>MCOLN1 (mucopolipin 1)</i> (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	<i>MTHFR (5,10-methylenetetrahydrofolate reductase)</i> (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292	<i>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2)</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	known familial variants
81294	duplication/deletion variants
81295	<i>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1)</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	known familial variants

CODES	DESCRIPTION
81297	duplication/deletion variants
81298	<i>MSH6</i> (<i>mutS</i> homolog 6 [<i>E. coli</i>]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	known familial variants
81300	duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81302	<i>MECP2</i> (<i>methyl CpG binding protein 2</i>) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	known familial variant
81304	duplication/deletion variants
81317	<i>PMS2</i> (<i>postmeiotic segregation increased 2</i> [<i>S. cerevisiae</i>]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	known familial variants
81319	duplication/deletion variants
81321	<i>PTEN</i> (<i>phosphatase and tensin homolog</i>) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	known familial variant
81323	duplication/deletion variants
81324	<i>PMP22</i> (<i>peripheral myelin protein 22</i>) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	full sequence analysis
81326	known familial variant
81330	<i>SMPD1</i> (<i>sphingomyelin phosphodiesterase 1, acid lysosomal</i>) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	<i>SNRPN/UBE3A</i> (<i>small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A</i>) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	<i>SERPINA1</i> (<i>serpin peptidase inhibitor, clade A, alpha-1-antitrypsin, member 1</i>) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
HCPCS Level II Codes	
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von hippel-lindau disease
S3844	DNA analysis of the connexin 26 gene (<i>gjb2</i>) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin e beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3852	DNA analysis for apoe epsilon 4 allele for susceptibility to Alzheimer's disease
S3853	Genetic testing for myotonic muscular dystrophy
S3861	Genetic testing, sodium channel, voltage-gated, type v, alpha subunit (<i>scn5a</i>) and variants for suspected brugada syndrome

CODES	DESCRIPTION
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

Note: Inclusion on this list does not guarantee coverage

DRAFT

Appendix C. HERC Guidance Development Framework

Validated questionnaire to assess genetic risk in all pregnant women

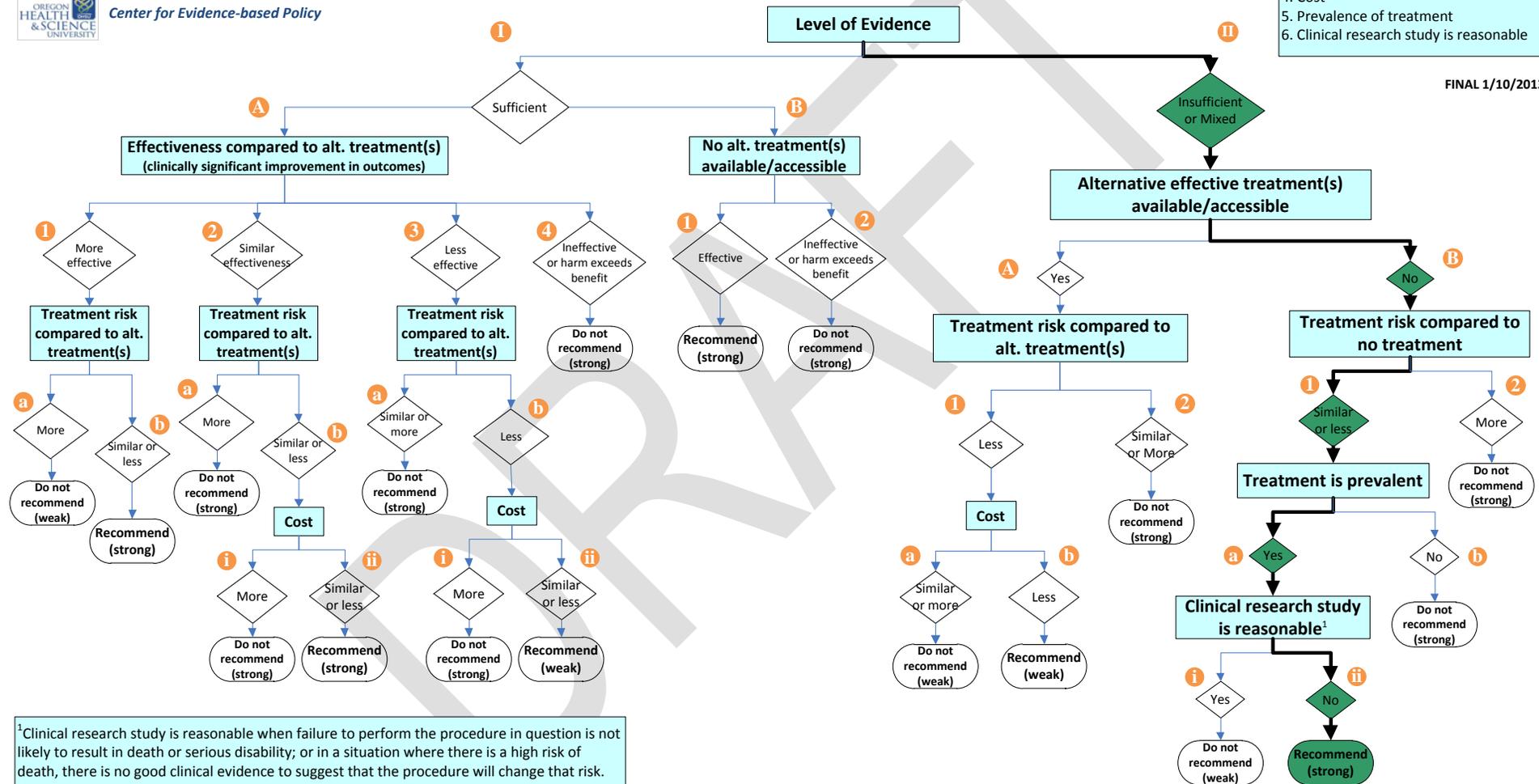


HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Aneuploidy testing with QF-PCR; Aneuploidy testing with FISH



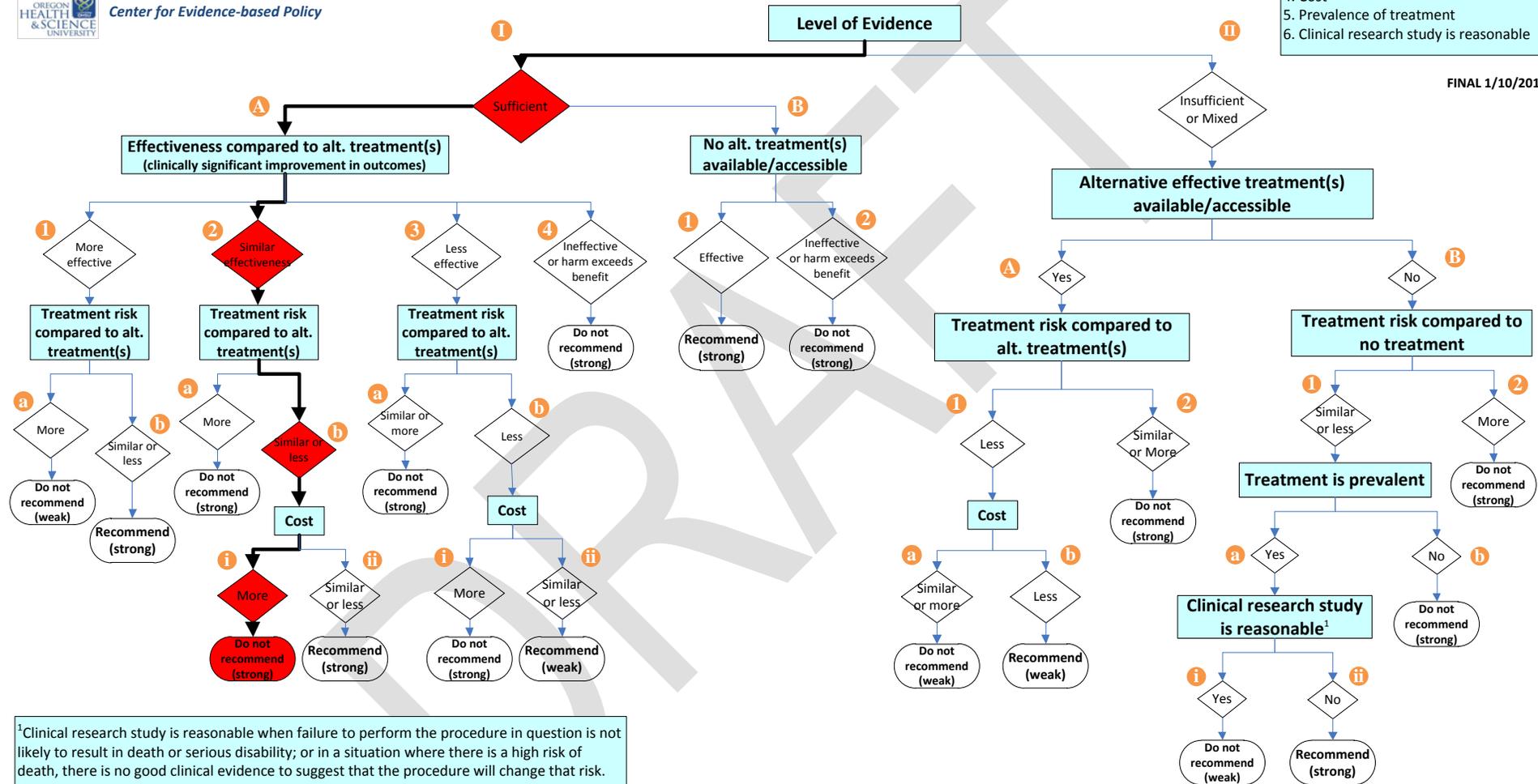
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**

 1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Cell free fetal DNA testing



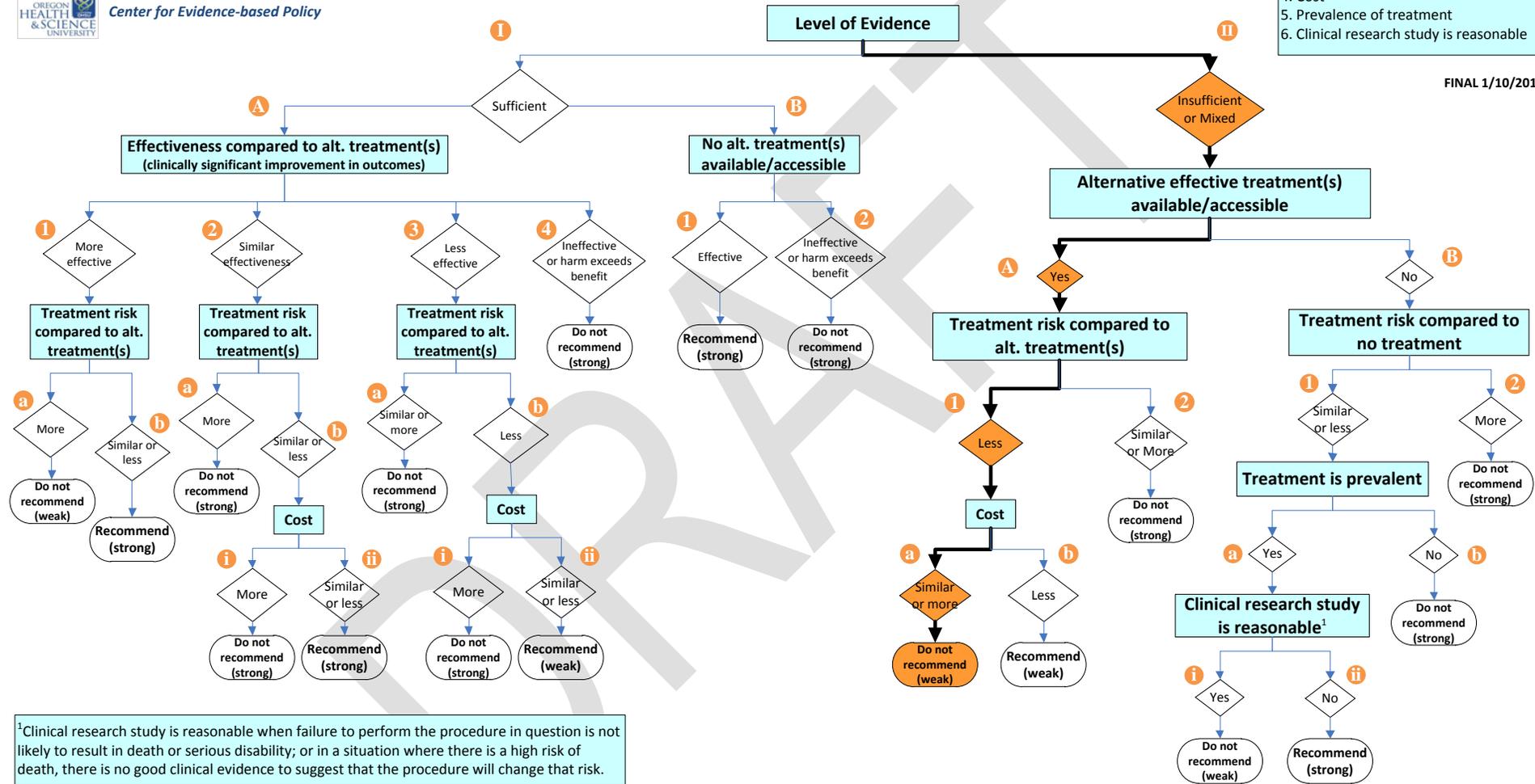
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**

 1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Ultrasound for structural anomaly screen at 18-20 weeks; Fetal genetic analysis of fetuses at risk for fetal skeletal dysplasia based on US; Spinal muscular atrophy carrier screening

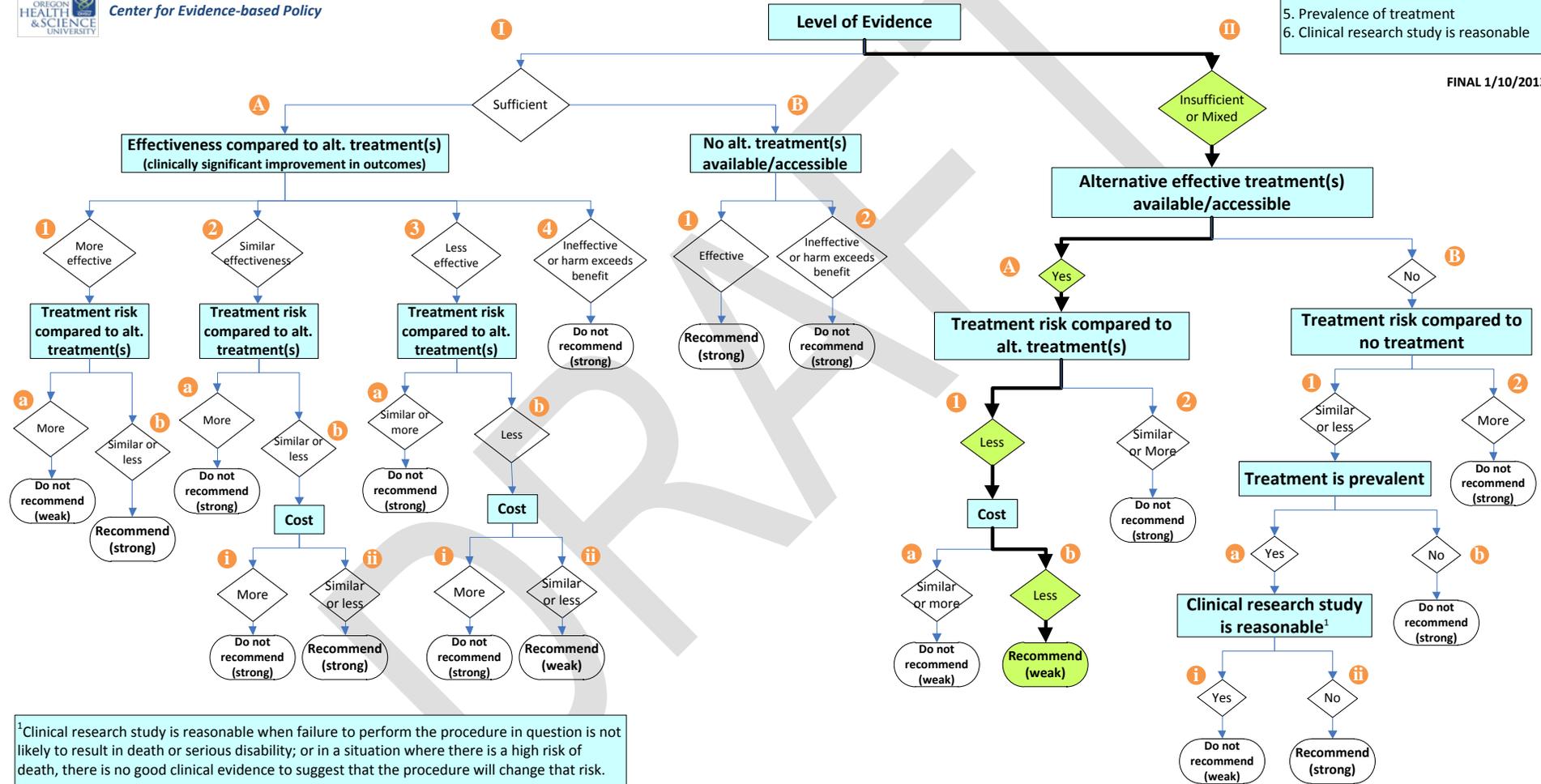


HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN

DRAFT for EbGS meeting materials 6/6/2013

HERC COVERAGE GUIDANCE

Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders¹, including those at risk for ADHD, specific parent behavior training² is recommended for coverage as first-line therapy (*strong recommendation*).

Pharmacotherapy³ is recommended for coverage as a second line therapy (*weak recommendation*).

If parent behavior training is not available, or contraindicated, and medication is not desired, coverage is recommended for other types of behavioral or psychosocial treatments (weak recommendation).

Provider consultation with teachers is recommended for coverage (*weak recommendation*)

Children Age 6 and Over

For children 6 and over diagnosed with ADHD¹, pharmacotherapy³ alone (*weak recommendation*) or pharmacotherapy³ with psychosocial/behavioral treatment (*strong recommendation*) are considered first-line therapy and are recommended for coverage. *Behavioral/ psychosocial treatment and parent behavior training alone are not recommended for coverage for moderate or severe ADHD¹ (weak recommendation)*

Provider consultation with teachers is recommended for coverage (*weak recommendation*)

¹ Children with comorbid mental health conditions may require additional or different treatments that are not addressed in this guidance.

² Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program. The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.

³ Limited to medications that are FDA-approved for the condition.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

American Academy of Pediatrics (AAP). (2011). Supplemental information. Implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. *Pediatrics*, S11-S121. Retrieved December 5, 2012, from <http://pediatrics.aappublications.org/content/128/5/1007/suppl/DC1>

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, overactivity, and impulsivity. While ADHD can begin before children enter

school, it is most commonly identified and treated in primary school. Boys are classified with ADHD approximately twice as frequently as girls, and primary school-age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a “disorder” to a greater or lesser degree. Symptoms are clinically significant when they cause impaired functioning. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive.

Although the condition now classified as ADHD was first described clinically in 1902, few treatments were available until the 1950s, when methylphenidate (brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder. The diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America. By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002% of the U.S. child population at that time. In contrast, the U.S. National Survey of Child Health provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8% of that population, of which 2.5 million (56%) were receiving medication. Within the United States, the estimated prevalence of adult ADHD stands at 4.4%. Prescriptions for the treatment of ADHD have increased as well, with methylphenidate prescriptions increasing from 4 million to 11 million, and prescriptions for amphetamines increasing from 1.3 million to 6 million in an eight year period of time (1991-1999).

Drugs currently FDA approved for treatment of ADHD and their maximum recommended daily dosages are listed in Table 1. In addition, a variety of antidepressants are used off-label to treat this condition.

Table 1. FDA Approved Medications for the Treatment of ADHD

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
<i>Amphetamine preparations</i>		
Mixed amphetamine salts	Adderall	40mg
	Adderall XR	30mg
Dextroamphetamine	Dexedrine, Dextrostat	40mg
	Dexedrine spanule	40 mg
Lisdexamfetamine	Vyvanse	70mg
<i>Methylphenidate preparations</i>		
Dexmethylphenidate	Focalin	20mg

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
	Focalin XR	30mg
Methylphenidate HCL	Methylin, Ritalin, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER	60mg
	Daytrana	30mg
	Concerta	54mg < 13 years/ 72mg ≥ 13 years ¹
SNRIs		
Atomoxetine	Strattera	1.4mg/kg or 100mg
Other		
Guanfacine extended release	Intuniv	4mg
Clonidine extended release	Kapvay	0.4mg/day

Evidence Review

The purpose of this review is to critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD and to similarly examine the comparative long-term effectiveness and adverse events of interventions for ADHD.

Treatment of Preschoolers with Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD², evidence was grouped into two broad categories of treatment: behavioral interventions and psychostimulant medication. A total of 31 studies evaluated parent behavior training, which was primarily defined as one of four manualized programs³. Nearly all studies showed positive effects, and pooled results for eight good-quality studies also found a significant improvement in

¹ From AAP 2011 reference

² The ADHD diagnosis has not been widely applied in children under age 6 because of uncertainty regarding the reliability and validity of the diagnostic criteria in this age group. Because ADHD in this age group is commonly identified in the context of other disruptive behaviors, and in children with diagnoses of Disruptive Behavior Disorders including Oppositional Defiant Disorder and Conduct Disorder, the evidence review includes studies of children less than six with Disruptive Behavior Disorders.

³ Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program

child behavior with parent behavior training. In addition, the single good-quality study of methylphenidate finds that it appears to be effective. The strength of evidence for use of parent behavior training was judged high due to number of studies and consistency of results. The strength of evidence for methylphenidate was judged low because there is only one good-quality study.

Long-term extension (follow-up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years, although no long-term study (lasting 12 months or more) of parent behavior training alone included untreated comparison groups, and attrition was high. A recent study examining parent behavior training with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of parent behavior training at two years. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorder and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources, although direct comparisons of identical interventions offered to families of different SES have not yet been performed. All behavioral interventions showed benefits relative to no-treatment controls, and a dose response to the number of parent behavior training sessions attended by parents was also identified, enhancing the overall strength of evidence for effectiveness of parent behavior training.

Several small, short-term trials of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe. In addition, the Preschool ADHD Treatment Study (PATs), a large, high quality trial funded by the National Institute of Mental Health also suggests that methylphenidate is effective for improving parent-rated child behavior in preschoolers. This multisite trial had multiple phases, beginning with 10 sessions of parent behavior training. The training was followed by an open label safety lead-in phase of a psychostimulant medication, then a titration phase, a cross-over phase and open-label maintenance phase that lasted 10 months. The PATs study offers information about both the potential benefits and limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth, and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication. These findings are supported by two additional “fair” quality RCTs.

In conclusion, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. This favors the use of parent behavior training for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents

The long-term effectiveness and safety (at least 12 months of treatment and/or follow up) of several psychostimulants (e.g., methylphenidate immediate release amphetamine, Osmotic-controlled Release Oral delivery System methylphenidate, dextroamphetamine, mixed amphetamine salts, atomoxetine, clonidine and guanfacine extended release) have all been examined prospectively in children and adolescents age 6 and over. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to three years, and few serious adverse events were noted, although guanfacine extended release appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry (12 of 21), there may be enhanced representations of effectiveness and safety. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time.

Fewer children experienced adverse events with methylphenidate than with dextroamphetamine. Concerns about adverse events led to discontinuation of medications for 15% to 20% of children age 6 and over using extended release mixed amphetamine salts. Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small. Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs. There are many similarities between methylphenidate immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to three years in adults. Discontinuation in children and teens appears to be higher (26%) due to ineffectiveness and lower (3%) due to adverse events than with other agents, although these are not direct comparisons. As with

psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases. There is only one study of a pharmacologic intervention over an extended time period (three years) in adults with ADHD, and that study found symptom improvement was maintained for those on atomoxetine, and discontinuation due to adverse events was somewhat higher for adults (11%) than for children (3%).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to two years; however, high rates (40% to 60%) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial six to eight months of treatment. A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects. Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia. Serious adverse events include syncope and clinically significant changes on electrocardiogram.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved.

Psychosocial and Behavioral Interventions, Alone and in Combination with Medication
Investigations comparing psychosocial/behavioral interventions, alone and in combination with psychostimulant medication management, showed that both medication and combined medication/behavioral treatment (including school-based interventions) are more effective in treating ADHD and oppositional defiant disorder symptoms than psychosocial or behavioral interventions alone. Psychosocial interventions in the four included trials included intensive behavioral treatment (parent behavior training, child-focused treatment and a school-based intervention), multimodal treatment (parent behavior training, behavior management training, family therapy and child social skills training), “behavior treatment” (undefined) and EEG biofeedback.

Longer Term Outcomes

Evaluation of long-term outcomes (five or more years follow up) following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7 to 9 years with DSM-IV ADHD, combined subtype. The best quality data come from the Multimodal Treatment of ADHD Study, which compared 14 months of management with immediate release methylphenidate to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. No clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at

three years or beyond. In contrast, a few long-term cohort studies lasting five years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement. No prospective studies have been designed to investigate the question of long-term functional outcomes directly. There appear to be long-term academic benefits with medication interventions in some domains.

In conclusion, the evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate and a single good study for atomoxetine. These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions. The evidence for other pharmaceutical agents is insufficient, as is the evidence pertaining to parent behavior training and academic interventions.

[\[Evidence Source\]](#)

Evidence Summary

For children under age six, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. Classroom teacher consultations in addition to parent behavior training are beneficial to children of lower socioeconomic status. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate.

In children age six and over, there is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with behavioral/psychosocial interventions. There is evidence for only the short-term effectiveness for other FDA approved medications and guanfacine, the latter of which has more frequent adverse events.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
Pharmacologic treatment age <6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Agree, allow for school/daycare consultation also	Pharmacotherapy is recommended for coverage as a second line therapy (<i>weak recommendation</i>)
Parent Behavior Training (PBT) age <6	net benefit without apparent harms	high	modest costs	likely moderate variability in parent preferences for treatment	Agree, allow for school/daycare consultation also	Specific parent behavior training is recommended for coverage as first-line therapy (<i>strong recommendation</i>)
Behavioral/ psychosocial treatment age <6 (excluding PBT)	no evidence	insufficient	modest costs	likely moderate variability in parent preferences for treatment	Would like this to be an option when PBT is not available or is contraindicated	<i>No recommendation</i>
Pharmacologic treatment alone and combined with behavioral/ psychosocial interventions age ≥ 6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Agree, allow for school/daycare consultation also. Other treatment may be indicated for co-morbid conditions	Pharmacotherapy alone (<i>weak recommendation</i>) or pharmacotherapy with psychosocial/ behavioral treatment (<i>strong recommendation</i>) are considered first-line therapy

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
						and are recommended for coverage
Behavioral/ psychosocial treatment alone, PBT, academic interventions age ≥ 6	unable to draw conclusions	insufficient	modest costs	likely moderate variability in parent preferences for treatment	May be indicated for comorbid conditions	Behavioral/ psychosocial treatment alone, PBT, academic interventions age ≥ 6 for primary ADHD are not recommended for coverage (<i>weak recommendation</i>)
School/ daycare based interventions	net benefit in those <6 of low SES, benefit in ≥ 6 as element of intensive behavioral treatment, no apparent harms	low	modest costs	likely minimal variability in parent preferences	Recommend adding school/daycare teacher consultation	School/daycare based interventions are outside the purview of this coverage guidance (<i>No recommendation</i>) Provider consultation with teachers is recommended for coverage (based on evidence of children <6 with low SES) (<i>weak recommendation</i>)

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Five quality measures were identified when searching the [National Quality Measures Clearinghouse](#). The Institute for Clinical Systems Improvement developed three measures around diagnosis and management of attention deficit hyperactivity disorder (ADHD) in primary care for school age children and adolescents: 1) Percentage of patients diagnosed with ADHD whose medical record contains documentation that the clinician discussed the need for school-based supports and educational service options for children with ADHD; 2) Percentage of patients treated with psychostimulant medication for the diagnosis of ADHD whose medical record contains documentation of a follow-up visit at least twice a year; and 3) Percentage of patients newly diagnosed with ADHD whose medical record contains documentation of DSM-IV-TR or DSM-PC criteria. These three measures have not been endorsed by the National Quality Forum (NQF).

The National Committee for Quality Assurance developed two HEDIS measures, which are both endorsed by the NQF: 1) Follow-up care for children prescribed ADHD medication (initiation phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with a practitioner with prescribing authority during the 30-day initiation phase; and 2) Follow-up care for children prescribed ADHD medication (continuation and maintenance [C&M] phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who remained on the medication for at least 210 days and who, in addition to the visit in the initiation phase, had at least two follow-up visits with a practitioner within 270 days (9 months) after the initiation phase ended.

Oregon's Coordinated Care Organizations' quality of care objectives include the following measure: Meet or exceed the 90th percentile national Medicaid benchmarks for follow up care for children on ADHD medication.

COMMITTEE DELIBERATIONS – EVIDENCE-BASED GUIDELINE SUBCOMMITTEE

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

DRAFT

Appendix A. GRADE Framework Description

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
312.9	Unspecified disturbance of conduct
314	Hyperkinetic syndrome of childhood
314.0	Attention deficit disorder of childhood
314.00	Attention deficit disorder without mention of hyperactivity
314.01	Attention deficit disorder with hyperactivity
314.1	Hyperkinesis with developmental delay
314.2	Hyperkinetic conduct disorder
314.8	Other specified manifestations of hyperkinetic syndrome
314.9	Unspecified hyperkinetic syndrome
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
90785	Interactive complexity, add-on code to be used in conjunction with codes for primary service
90791	Psychiatric diagnostic evaluation (no medical services)
90792	Psychiatric diagnostic evaluation (with medical services)
90832	Psychotherapy, 30 minutes with patient and/or family member
90834	Psychotherapy, 45 minutes with patient and/or family member
90837	Psychotherapy, 60 minutes with patient and/or family member
90839	Psychotherapy for crisis, first 60 minutes
90840	Add-on for each additional 30 minutes of psychotherapy for crisis, used in conjunction with code 90839
90845	Psychoanalysis
90846	Family psychotherapy without the patient present
90847	Family psychotherapy, conjoint psychotherapy with the patient present
90849	Multiple-family group psychotherapy
90853	Group psychotherapy (other than of a multiple-family group)
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services; used only as add-on to primary psychotherapy code
98960	Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; individual patient
98961	2-4 patients
98962	5-8 patients
99201	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the

CODES	DESCRIPTION
	presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 20 minutes face-to-face with the patient and/or family.
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 45 minutes face-to-face with the patient and/or family.
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem

CODES	DESCRIPTION
	focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 25 minutes face-to-face with the patient and/or family.
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99241	Office consultation for a new or established patient, which requires these 3 key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical

CODES	DESCRIPTION
	decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 80 minutes face-to-face with the patient and/or family.
HCPCS Codes	
H2027	Psychoeducational service, per 15 minutes
S9444	Parenting classes, non-physician provider, per session
S9482	Family stabilization services, per 15 minutes
T1027	Family training and counseling for child development, per 15 minutes

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework – ADHD Indications

Pharmacologic Treatment age <6 as 1st Line Therapy

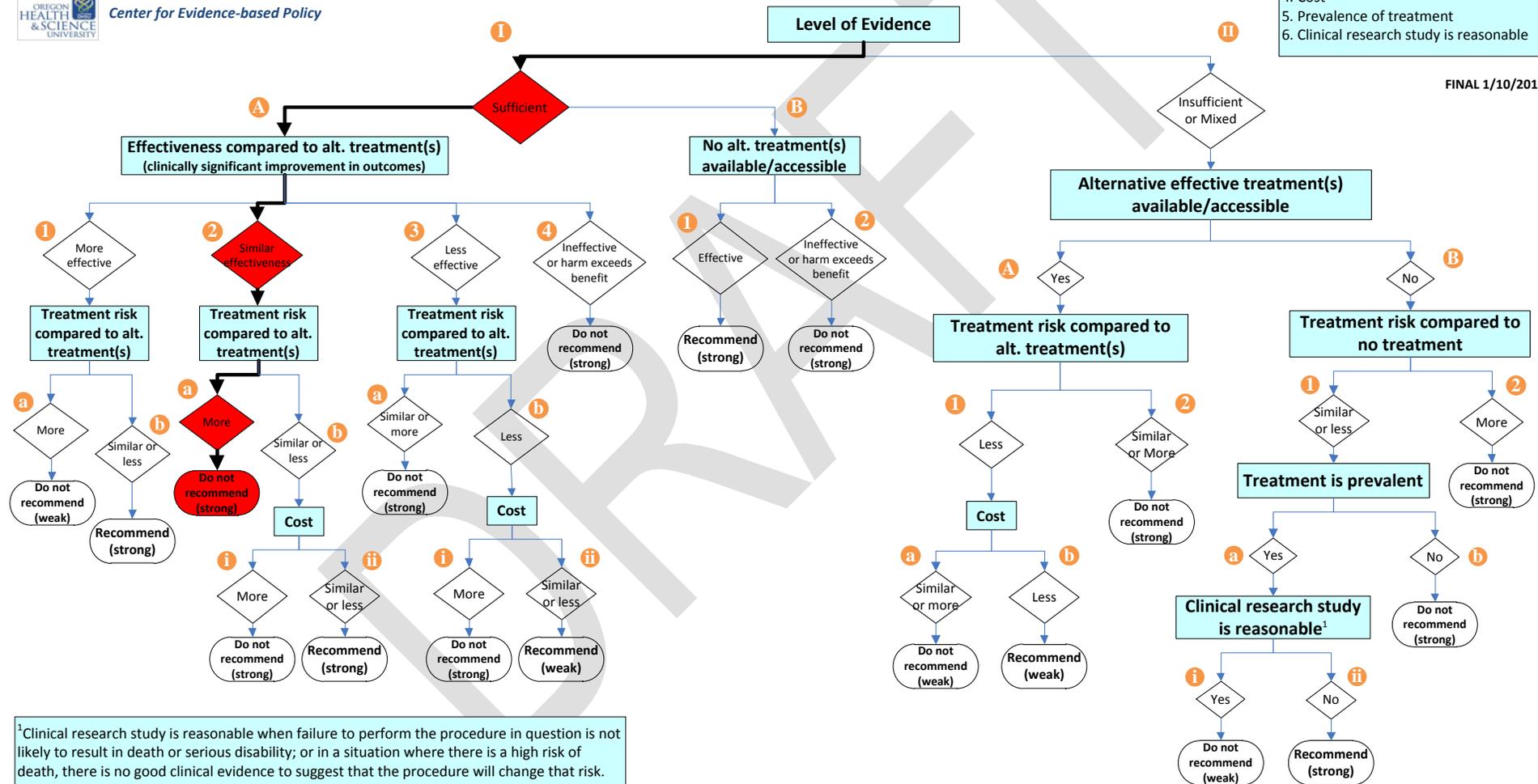


HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment age <6 as 2nd Line Therapy

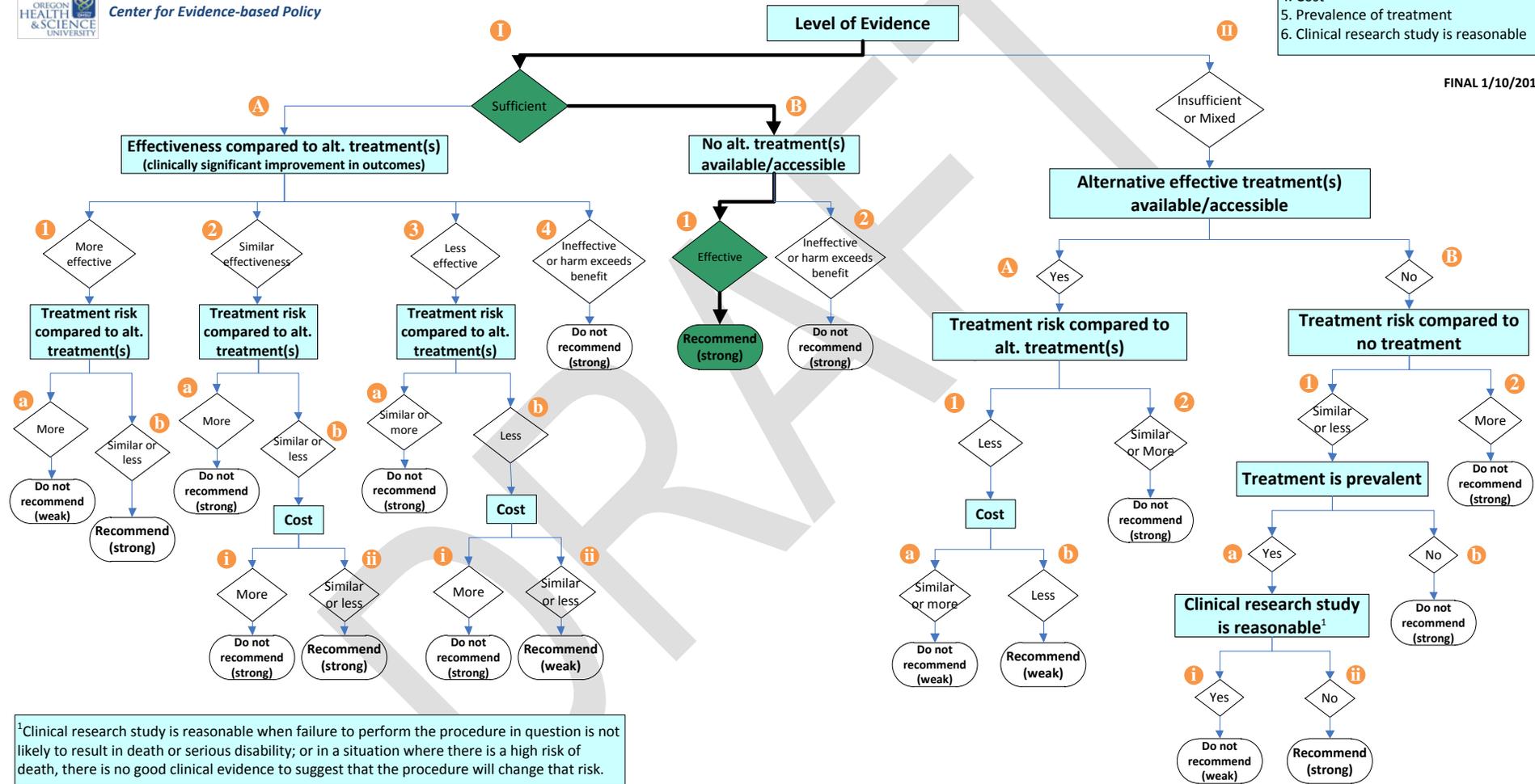


HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment Alone and Combined with Behavioral/Psychosocial Interventions Age ≥ 6



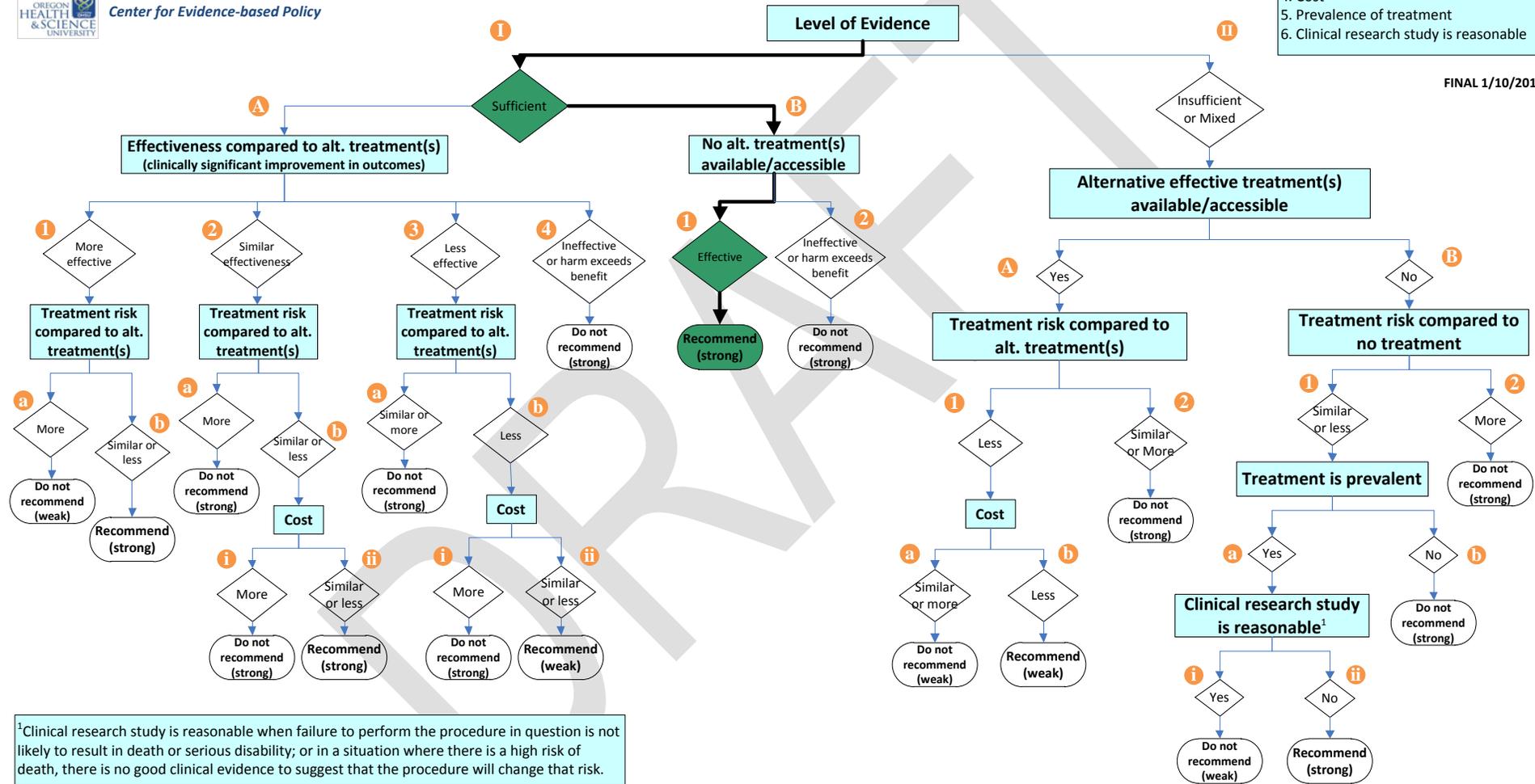
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**

 1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Behavioral/Psychosocial Treatment Alone, PBT, Academic Interventions Age ≥ 6 Compared to Pharmacologic Treatment

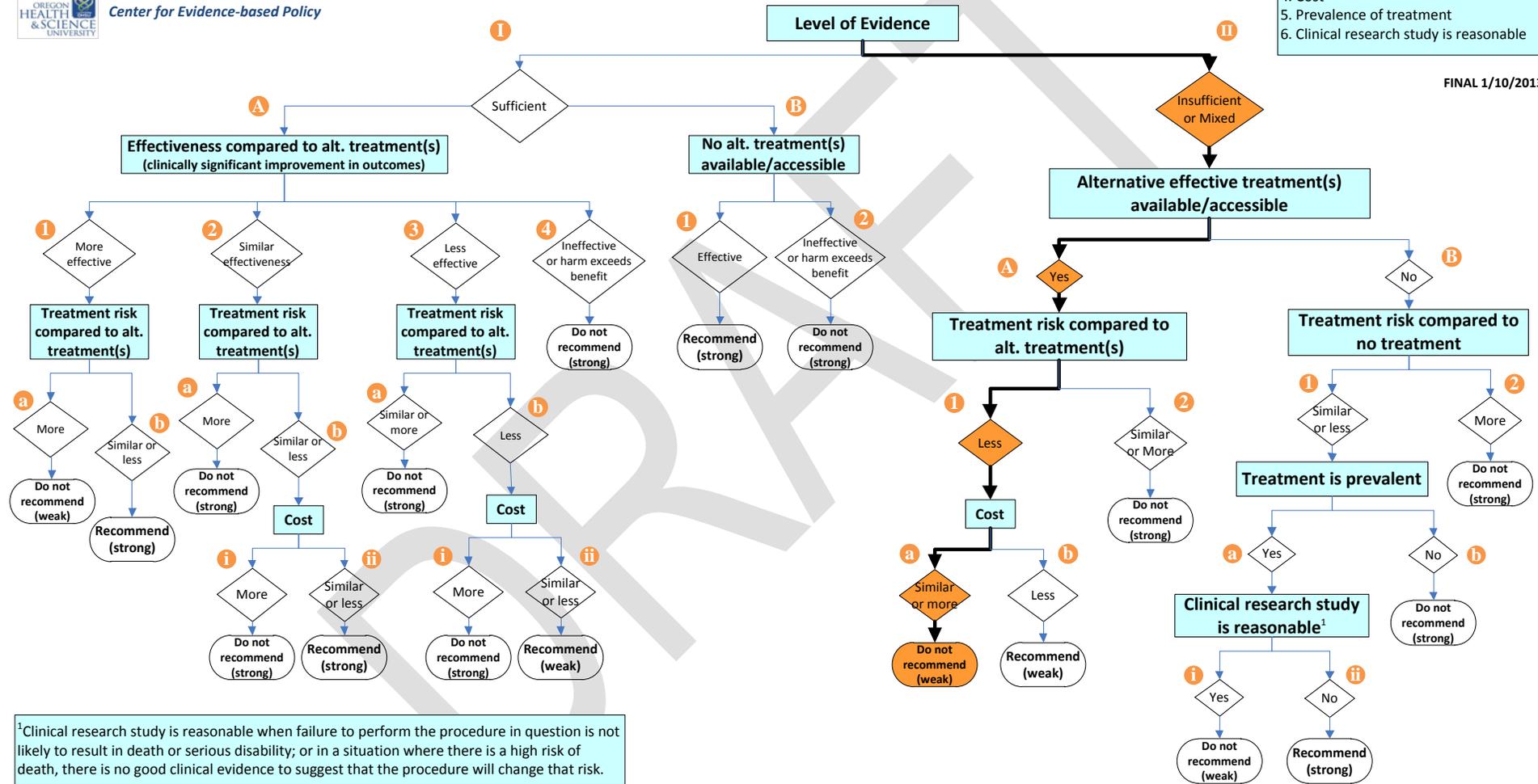


HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Review of references submitted by Beth Westbrook pertaining to treatment of ADHD

1. Attention-Deficit Hyperactivity Disorder in Children and Adults. Cambridge: Hogrefe & Huber. Advances in Psychotherapy – Evidence-based Practice series. Rickel, AU and Brown, RT. 2007

Unable to locate this book at OHSU Library. It was published in 2007, which is before the search dates of trusted sources.

2. Van der Ord, S and Bogels, SM: The effectiveness of mindfulness training for children with ADHD and mindful parenting for their parents. *Journal of Child and Family Studies*, 2007, 21: 139-147.

Small (N=22) trial that utilized wait-list control. Included both parent and child training groups. Most children were on stimulants. Outcomes measured via parent and teacher questionnaire. Children were 8-12 years of age. Found improved ratings from parents, no change in teacher ratings.

This study would fall into the category of medication plus psychosocial/behavioral for children > 6, which is already recommended for coverage.

3. Emilsson, B et al: Cognitive Behavior Therapy for medication-treated adults with ADHD and persistent symptoms: A randomized controlled trial. *BMJ Psychiatry* 2011, 11:116

Small (N=54) trial of adults with ADHD all of whom were receiving stimulant medication, randomized to CBT (Reasoning and Rehabilitation for ADHD Youths and Adults) or treatment as usual. Outcomes measured by clinician and patient self-report questionnaire. Found large effect sizes in the treatment group.

This study would fall into the category of medication plus psychosocial/behavioral for children > 6, which is already recommended for coverage.

4. Gevensleben, et al: Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. *Journal of Child Psychology and Psychiatry* (2009). Volume 50, Issue 7, July 2009, Pages: 780–789

The date of this study falls within the search dates for the AHRQ review. It was not listed as excluded, but would have been as it did not report outcomes after 12 months or more (one of the inclusion criterion for the review in patients older than 6). RCT (N=102) children aged 8-12, randomized to either neurofeedback or a computerized attention skills training (was meant to be the control). Outcomes measured by parent and teacher questionnaires, found moderate effect size difference in favor of neurofeedback at the end of training (training involved 36 sessions over 8-12 weeks). No evaluation after the final assessment which was one week after the final session.

While this RCT is supportive of neurofeedback, it is a single study with no long term follow up, and did not meet pre-specified criteria set forth by the trusted source.

5. Murray, DW: Treatment of Preschoolers with Attention-Deficit/Hyperactivity Disorder. *Curr Psychiatry Rep* (2010) 12:374-381

This is a narrative review of the literature pertaining to this topic. The author reaches the same conclusions as the AHRQ report; that parent behavior training is effective, that stimulants are effective, that there is no evidence for non-stimulants and that there is minimal research on other behavioral interventions. Discussion of multimodal psychological interventions reported only on two, one of which was parent behavior training in combination with classroom treatment, the other was the Incredible Years program.

The psychological interventions discussed were specified in guidance document and were recommended for coverage..

6. Am Acad of Pediatrics: ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics (2011) 128 (5) 1-16

This is a clinical practice guideline for this treatment of this disorder. Their recommendations for treatment align with the guidance document. The two key treatment recommendations pertaining to treatment state the following:

Action statement 5: Recommendations for treatment of children and youth with ADHD vary depending on the patient's age.

Action statement 5a: For *preschoolaged children (4–5 years of age)*, the primary care clinician should prescribe evidence-based parent and/or teacher-administered behavior therapy as the first line of treatment (quality of evidence A/strong recommendation) and may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. In areas in which evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (quality of evidence B/recommendation).

Action statement 5b: For *elementary school-aged children (6–11 years of age)*, the primary care clinician should prescribe FDA approved medications for ADHD (quality of evidence A/strong recommendation) and/or evidence based parent- and/or teacher administered behavior therapy as treatment for ADHD, preferably both (quality of evidence B/strong recommendation). The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended release guanfacine, and extended release clonidine (in that order) (quality of evidence A/strong recommendation). The school environment, program, or placement is a part of any treatment plan.

7. Scottish Intercollegiate Guidelines Network: Management of attention deficit and hyperkinetic disorders in children and young people: *A national clinical guideline*. (2009) www.sign.ac.uk

This is a guideline from one of the HERC's trusted sources. The recommendations align with the current guidance document. They are listed below:

Key recommendations

The following recommendations and good practice points were highlighted by the guideline development group as being clinically very important. They are the key clinical recommendations that should be prioritised for implementation. The clinical importance of these recommendations is not dependent on the strength of the supporting evidence.

Principles of intervention

Parents/carers of children with ADHD/HKD (*and older children with ADHD/HKD*) should be given information about ADHD/HKD and about possible interventions, including their potential risks and benefits. (good practice point)

There should be regular communication between health and education services to promote understanding of the difficulties of ADHD/HKD, to ensure a consistent approach to the individual across settings and to monitor effectiveness of intervention(s). (good practice point)

Psychological interventions

Behavioural parent training is recommended for parents of pre-school children with symptoms of ADHD/HKD. This should be delivered by trained facilitators. (level of evidence B)

Treatment selection

For school aged children and young people with hyperkinetic disorder (*severe ADHD*) medication is recommended. (level of evidence A)

For school aged children and young people with ADHD /HKD and comorbid symptoms of oppositional defiant disorder and/or aggressive behaviour a combination of medication and behavioural treatments is recommended. (level of evidence A)

For school aged children and young people with ADHD /HKD and comorbid generalised anxiety disorders a combination of medication and behavioural treatments is recommended. (level of evidence B)

Where symptoms of ADHD are mild, clinicians should consider behavioural approaches in the first instance. (good practice point)

MEDLINE SEARCH UPDATE FOR ADHD COVERAGE GUIDANCE LIMITED TO PRESCHOOL AGED CHILDREN

A search of MEDLINE was conducted at the request of EbGS clinical staff to evaluate whether there was any evidence pertaining to psychological or behavior therapy in preschool aged children that had been published since the AHRQ review that served as the evidence report for the ADHD coverage guidance document. That review searched multiple databases; however this task involved searching only MEDLINE. The search strategy that was used in the base report was modified for this addendum, with the following changes:

- Limited to preschool (age <6)
- No limitation on study design (except exclusion of commentaries/letters) – AHRQ excluded reviews and meta-analyses
- Limited date range to studies published after AHRQ search date
- Used Psychotherapy MeSH term, which includes behavioral treatments
- Excluded pharmacologic interventions

A total of 111 citations were retrieved and reviewed. Thirty-five pertained to parent behavior training; most others pertained to an unrelated topic or a different age group. Three potentially relevant citations were identified:

- Sonuga-Barke (2013) – This review had been identified earlier. It includes ages up to 18. Included psychological interventions were cognitive training, neurofeedback and behavioral interventions; however the only studies that address the age group of interest all pertained to parent behavior training.
- Conway (2012) – This review is described as systematic, and reports identifying “23 case studies, research reports, and theoretical writings. Questions relevant to the practice of psychodynamic psychotherapy were the focus and included a review of psychodynamic diagnosis of ADHD, theoretical orientations of psychodynamic psychotherapy, identification of core treatment issues, clinical examples, and theoretical perspectives on therapeutic change as well as practice techniques”. It includes children up to age 18 but identifies the following studies on preschool children:
 - Fonagy & Target (1994) – Included up to age 18, but specifies that it also includes age <6 (N not specified by age group). This was a retrospective

chart review, not a comparative study, N=763 for all ages, interventions described as “mirroring, reflecting, mentalize, social scaffolding, interpretation of transference”. Does not describe efficacy of these interventions or any outcomes.

- Leuzinger-Bohleber (2011) – Age 3-6 – N=40, children had comorbid conditions
- Li (2010) – This RCT combined electro-acupuncture and behavior therapy. The latter was delivered to both groups, was tailored to patient symptoms; methods included positive reinforcement, punishment, extinction, token replacement, etc. Therapy was delivered 30 minutes after the electro-acupuncture for 40 minutes, daily for six days, and then repeated for a total of 12 weeks. While there was improvement in both groups, the improvement over baseline was not tested statistically in either group, so the efficacy of behavioral therapy could not be determined.

References

- Conway, F. (2012). Psychodynamic psychotherapy of ADHD: a review of the literature. *Psychotherapy: Theory, Research, Practice, Training*, 49(3), 404-417.
- Fonagy, P., & Target, M. (1994). The efficacy of psychoanalysis for children with disruptive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 33(1), 45–55.
- Leuzinger-Bohleber, M., Laezer, K. L., Pfenning-Meerkoetter, N., Fischmann, T., Wolff, A., & Green, J. (2011). Psychoanalytic treatment of ADHD children in the frame of two extraclinical studies: The Frankfurt Prevention Study and the EVA Study. *Journal of Infant, Child and Adolescent Psychotherapy*, 10, 32–50.
- Li, S., Yu, B., Lin, Z., Jiang, S., He, J., Kang, L., et al. (2010). Randomized-controlled study of treating attention deficit hyperactivity disorder of preschool children with combined electro-acupuncture and behavior therapy. *Complementary Therapies in Medicine*, 18(5), 175-183.
- Sonuga-Barke, E.J., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., & Holtmann, M. (2013). Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments. *American Journal of Psychiatry*, 170(3), 275-289.

HERC ADHD Treatment Search Strategy – OVID-Medline (Search date: 5/13/2013)

1. "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/
2. minimal brain d?sfuction*.tw,sh.
3. (attention deficit* or adhd).tw.
4. addh.tw.
5. or/1-4
6. Hyperkinesis/
7. Impulsive Behavior/
8. Child Behavior Disorders/
9. aggression/ or agonistic behavior/
10. inattent*.tw.
11. Impulse Control Disorders/
12. (disruptive adj4 disorder?).tw.
13. or/6-12
14. exp *Mental Disorders/
15. (attention deficit* or adhd).tw.
16. hyperactiv*.tw.
17. inattent*.tw.
18. Impulsive Behavior/
19. 15 or 16 or 17 or 18
20. 14 and 19
21. 5 or 13 or 20
22. limit 21 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
23. exp Child, Preschool/
24. 21 and 23
25. 22 or 24
26. (comment or editorial or letter).pt.
27. 25 not 26
28. limit 27 to yr="2010 -Current"
29. limit 28 to humans
30. limit 29 to english language
31. exp Psychotherapy/
32. 30 and 31

ARHQ ADHD Treatment Search Strategy – OVID-Medline (Search date: 5/31/2010)

1. "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/
2. minimal brain d?sfuction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. Hyperkinesis/
7. Impulsive Behavior/
8. Child Behavior Disorders/
9. aggression/ or agonistic behavior/
10. inattent*.tw.
11. Impulse Control Disorders/
12. (disruptive adj4 disorder?).tw.
13. or/6-12
14. limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
15. exp *Mental Disorders/
16. (attention deficit* or adhd).tw.
17. hyperactiv*.tw.
18. inattent*.tw.
19. Impulsive Behavior/
20. or/16-19
21. 15 and 20
22. 5 or 21
23. limit 22 to yr = "1997 -Current"
24. 14 or 23
25. Drug Therapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
26. (side effect? or adverse or harm?).tw.
27. atomoxetine.tw.
28. guanfacine.tw.
29. Lisdexamfetamine.tw.
30. Vyvanse.tw.
31. exp Central Nervous System Stimulants/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]
32. ritalin.tw.
33. or/25-32
34. (attention deficit* or adhd).tw.

35. 33 and 34
36. 24 or 35
37. (comment or editorial or letter).pt.
38. 36 not 37
39. review.pt,sh.
40. 38 and 39
41. meta-analysis.pt,ti,ab,sh.
42. (meta anal\$ or metaanal\$).ti,ab,sh.
43. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
44. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
45. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
46. (medline or embase or cochrane).ti,ab.
47. or/44-46
48. review.pt,sh.
49. 47 and 48
50. 41 or 49 or 43 or 42
51. 38 and 50
52. 40 not 51
53. 38 not 52
54. limit 53 to humans
55. limit 54 to english language