HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PRENATAL GENETIC TESTING

Approved 3/2014 with DRAFT corrections for November 13, 2014 HERC meeting

HERC COVERAGE GUIDANCE

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

- Genetic counseling for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect
- Genetic counseling prior to consideration of 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 five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency]
- Ultrasound for structural anomalies between 18 and 20 weeks gestation
- CVS or amniocentesis for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
- 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 personal or family history of
    - fragile X tremor/ataxia syndrome
    - premature ovarian failure
    - unexplained early onset intellectual disability
    - fragile X intellectual disability
    - 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, familial dysautonomia, Tay-Sachs carrier status and cystic fibrosis carrier status.
- Expanded carrier screening only for those genetic conditions identified above

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

- Cell free fetal DNA testing for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening)

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

- Serum triple screen
- Screening for thrombophilia in general population or for recurrent pregnancy loss
- Expanded carrier screening which includes results for conditions not explicitly recommended 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 Heath 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

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). (2013). Sequencing-based tests to determine fetal trisomy 21 from maternal plasma DNA. *TEC Assessment Program, 27*(10). Retrieved September 20, 2013 from http://www.bcbs.com/blueresources/tec/vols/27/sequencing-based-tests-to.html

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	**First choice (for women who enter care in the first trimester)**: nuchal translucency (NT), beta-human chorionic gonadotropin (beta-hCG), and	**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	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
[4] See below for description of these screening strategies

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
	pregnancy-associated plasma protein A (PAPP-A) (11 weeks 0 days and 13 weeks 6 days); **Second choice (for women who present later in the pregnancy)**: triple[2] or quadruple[3] test (15 weeks 0 days and 20 weeks 0 days).	ultrasound assessment, first-trimester chorionic villus sampling and second-trimester amniocentesis. **If first trimester screening is elected:** second-trimester serum AFP screening and/or US should be offered to screen for open neural tube 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 thallasemia carriers	Maternal request Offer CVS in first trimester if: • 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: • Abnormal first or second	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

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

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
		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	(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 in the MED report. One guideline recommends that cell free DNA testing be offered to patients at increased risk of aneuploidy[5]. They recommend that it NOT be a part of routine prenatal laboratory measurements or be offered to low risk women.

The Blue Cross TEC Assessment Program analyzed this technology and identified eight studies that reported on the performance of cff-DNA for trisomy 21 screening in singleton high-risk pregnancies. They found that cff-DNA testing reduced the number of invasive confirmatory procedures needed and consequent associated miscarriages, while improving the number of detected cases of trisomy 21, compared to standard screening procedures in high-risk populations of pregnant women. They therefore concluded that ccf-DNA meets the TEC criteria.

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 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

[5] Maternal age ≥ 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

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

screening[6], 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.

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

[6] Testing relatives of Fragile X patients to determine carrier status

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, Mucolipidosis 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. The 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. Cell free DNA testing reduces the

number of invasive confirmatory procedures needed while improving the number of detected cases of trisomy 21, compared to standard screening procedures, in high-risk populations of pregnant women.

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.

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	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 *(weak recommendation)*
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 *(weak recommendation)*
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 *(weak recommendation)* Serum triple screen is not recommended for coverage *(weak recommendation)*

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
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 *(weak recommendation)*
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	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 *(weak recommendation)* Genetic counseling is recommended for coverage prior to CVS/amniocentesis *(weak recommendation)*
Aneuploidy testing with QF-PCR	Similar risk to karyotyping, may be more beneficial when rapid turnaround is required	None	Moderate	High variability	*Test not available in the US – no recommendation made*
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, resulting in increased maternal anxiety	Low	Moderate	Limited variability (because anomalies already identified)	Recommended for coverage when major fetal congenital anomalies apparent on imaging and karyotype is normal *(weak recommendation)*

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
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)	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 *(weak recommendation)*
Cell free fetal DNA testing	High level of accuracy (98% detection rate with false positive < 0.5%). Less risk than karyotyping but less information provided (current tests only identify trisomy 13, 18 and 21)	~~None~~Moderate	High	Moderate variability (many women would choose a noninvasive highly accurate test)	Cell free fetal DNA testing is ~~not~~ recommended for coverage *(~~weak~~strong recommendation)*
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)	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 *(weak recommendation)*

[7] Ashkenazi Jewish, French Canadian and Cajun

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Screening for CF carrier status	Potential benefit, minimal harm	Moderate	Moderate	Moderate variability	Screening for cystic fibrosis status is recommended for coverage once in a lifetime *(weak recommendation)*
Screening for fragile X carrier status in women with +FH or risk factors[8]	Small benefit, depending on values of parents, minimal harm	Low	Moderate	Moderate variability	Screening for fragile X status in patients with a personal or family history of • fragile X tremor/ataxia syndrome • premature ovarian failure • unexplained early onset intellectual disability • fragile X intellectual disability • unexplained autism through the pregnant woman's maternal line adult
Screening for thrombophilia	No definite benefit, possible harm if prophylactic treatment undertaken (bleeding risks from anticoagulation)	Low	Moderate (if treatment undertaken)	Limited	Screening for thrombophilia is not recommended for coverage for recurrent pregnancy loss <u>or in the general population</u> (*weak recommendation*)
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	*No recommendation made*

[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	Coverage Recommendation
Spinal muscular atrophy carrier screening	Small benefit, depending on values of parents, minimal harm	None	Low	Moderate variability	Screening for spinal muscular atrophy is recommended for coverage once in a lifetime *(weak recommendation)*
Screening of Ashkenazi Jewish population for specific genetic diseases	Likely beneficial, minimal risks	Low	Moderate	Moderate variability	Screening is recommended for coverage for those of Ashkenazi Jewish heritage for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia *(weak recommendation)*
Expanded carrier screening	Components likely beneficial, however, there is a risk of cascade testing, clinically unimportant results	None	Moderate. There is a cascade of testing. However, compared to individual diagnostic tests, this type of testing is much less expensive	High variability	Coverage is recommended for expanded carrier screening only for those genetic conditions previously identified with enough evidence or guidelines to support a recommendation for coverage *(weak recommendation)* Coverage is not recommended for an unlimited variety of tests offered as part of expanded carrier screening *(weak recommendation)*
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)	Pretest genetic counseling is recommended for coverage prior to CVS, amniocentesis, Fragile X, microarray, and spinal muscular atrophy screening *(weak recommendation)*

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

In its review of this topic at its meetings April 4, June 6 and September 7, 2013, EbGS reviewed the initial draft coverage guidance and made the following decisions (some decisions from early meetings were later reversed; the final decisions are reflected here):

- Did not include coverage for CVS/Amniocentesis for the indication of 'on maternal request' as a weak recommendation.
- Made no recommendation on QF-PCR as the test is not available in the United States.
- Recommended coverage for genetic counseling for women with certain risk factors.
- 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.
- Decided to recommend coverage for Cell Free Fetal DNA testing for high risk pregnancies based on new evidence from trusted sources which was submitted during public comment.
- Changed the recommendation for thrombophilia screening to clarify that it is not recommended for screening, or for women with a history of recurrent pregnancy loss.
- Recommended coverage for spinal muscular atrophy only once in a lifetime with pretest genetic counseling.
- Recommended coverage for carrier screening in the Ashkenazi Jewish population for only four conditions rather than eight.

COMMITTEE DELIBERATIONS – VBBS

VbBS discussed the draft coverage guidance at its meeting 10/10/2013, reviewing a guideline note based on the draft coverage guidance. The subcommittee asked staff to consult with experts to incorporate the correct procedure codes into the guideline note, and added wording to allow a broader, but less expensive, test panel for additional

testing specific to patients of Ashkenazi Jewish heritage. However, with regard to expanded carrier screening, the subcommittee chose not to make a similar statement, as some test panels currently available include traits such as eye color, and could be clinically irrelevant or inappropriate.

COMMITTEE DELIBERATIONS – HERC

The Health Evidence Review Commission reviewed the draft coverage guidance on March 13, 2014. The commission modified the criteria for coverage of genetic counseling prior to CVS, amniocentesis, microarray testing, Fragile X and spinal muscular atrophy screening to include patients considering those tests.

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~~76805	~~DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed~~Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
76810	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; each additional gestation
76811	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation
76812	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; each additional gestation
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
76814	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation
76817	Ultrasound, pregnant uterus, real time with image documentation, transvaginal
81200	*ASPA (aspartoacylase)* (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
~~81205~~	~~*BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)* (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)~~
81209	*BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant)

CODES	DESCRIPTION
81220	*CFTR (cystic fibrosis transmembrane conductance regulator)* (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~~	~~*CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)~~
~~81226~~	~~*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5,*6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)~~
~~81227~~	~~*CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)~~
81228	~~Cytrogenomic~~Cytogenomic 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 polymorphism (SNP) variants for chromosomal abnormalities
~~81240~~	~~*F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant~~
~~81241~~	~~*F5 (coagulation Factor V) (eg, hereditary hypercoagulability)* gene analysis, Leiden variant~~
81242	*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	*FMR1 (Fragile X mental retardation 1)* (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~~	~~*G6PC (glucose-6-phosphatase, catalytic subunit)* (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)~~
81251	*GBA (glucosidase, beta, acid)* (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
~~81252~~	~~*GJB2 (gap junction protein, beta 2, 26kDa, conexin 26)* (eg, nonsyndromic hearing loss) gene analysis; full gene sequence~~
~~81253~~	~~known familial variants~~
~~81254~~	~~*GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)* (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])~~
81255	*HEXA (hexosaminidase A [alpha polypeptide])* (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
~~81256~~	~~*HFE (hemochromatosis) (eg, hereditary hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)~~
81257	*HBA1/HBA2 (alpha globin 1 and alphaglobin 2)* (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)

CODES	DESCRIPTION
81260	*IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)* (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
~~81280~~	~~Long QT syndrome gene analyses (eg, *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2*); full sequence analysis~~
~~81281~~	~~known familial sequence variant~~
~~81282~~	~~duplication/deletion variants~~
81290	*MCOLN1 (mucolipin 1)* (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
~~81291~~	~~*MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)~~
~~81292~~81507	~~*MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2)* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis~~Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as risk score for each trisomy
~~81293~~	~~known familial variants~~
~~81294~~	~~duplication/deletion variants~~
~~81295~~	~~*MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1)* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis~~
~~81296~~	~~known familial variants~~
~~81297~~	~~duplication/deletion variants~~
~~81298~~	~~*MSH6 (mutS homolog 6 [E. coli])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis~~
~~81299~~	~~known familial variants~~
~~81300~~	~~duplication/deletion variants~~
~~81301~~81508	~~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~~Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
~~81302~~	~~*MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome) gene analysis; full sequence analysis~~
~~81303~~	~~known familial variant~~
~~81304~~	~~duplication/deletion variants~~
~~81317~~	~~*PMS2 (postmeiotic segregation increased 2 [S. cerevisiae])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis~~
~~81318~~	~~known familial variants~~
~~81319~~	~~duplication/deletion variants~~
~~81321~~	~~*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis~~
~~81322~~	~~known familial variant~~
~~81323~~	~~duplication/deletion variants~~

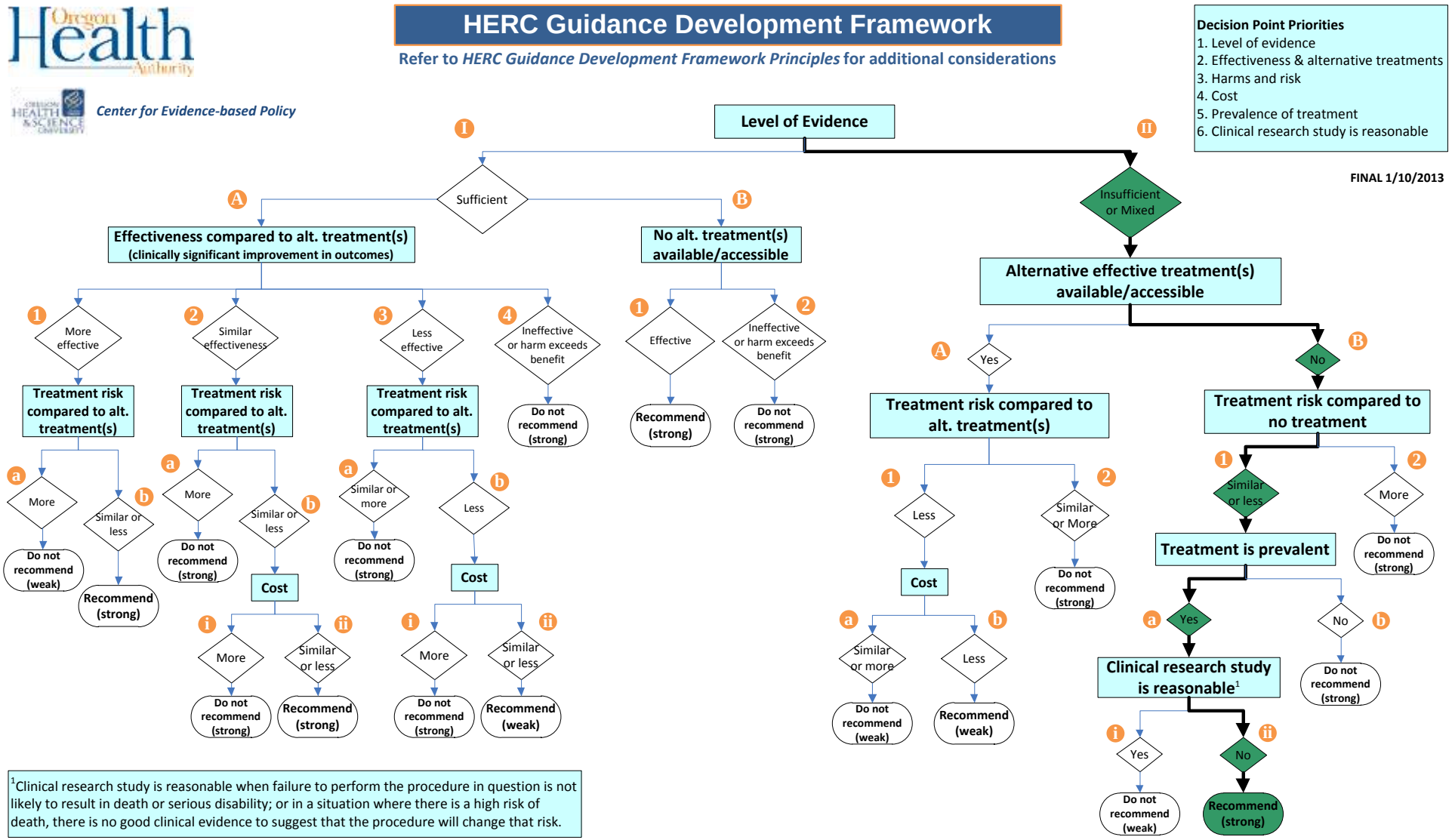
CODES	DESCRIPTION
~~81324~~	~~*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis~~
~~81325~~	~~full sequence analysis~~
~~81326~~	~~known familial variant~~
~~81330~~81509	~~*SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal)* (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)~~Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score
~~81331~~81510	~~*SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis~~Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
~~81332~~81511	~~*SERPINA1 (serpin peptidase inhibitor, cladeA, alpha-1-antiproteinase, antitrypsin, member 1)* (eg, alpha-1-antitruypsin deficiency), gene analysis, common variants (eg, *S and *Z)~~Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	interphase in situ hybridization, analyze 25-99 cells
88275	interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	additional specialized banding technique (eg, NOR, C-banding)
88285	additional cells counted, each study
88289	additional high resolution study
88291	Cytogenetics and molecular cytogenetics, interpretation and report
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 (gjb2) 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~~

CODES	DESCRIPTION
~~S3853~~	~~Genetic testing for myotonic muscular dystrophy~~
~~S3861~~	~~Genetic testing, sodium channel, voltage-gated, type v, alpha subunit (scn5a) and variants for suspected brugada syndrome~~
~~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 hybrization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

Note: Inclusion on this list does not guarantee coverage

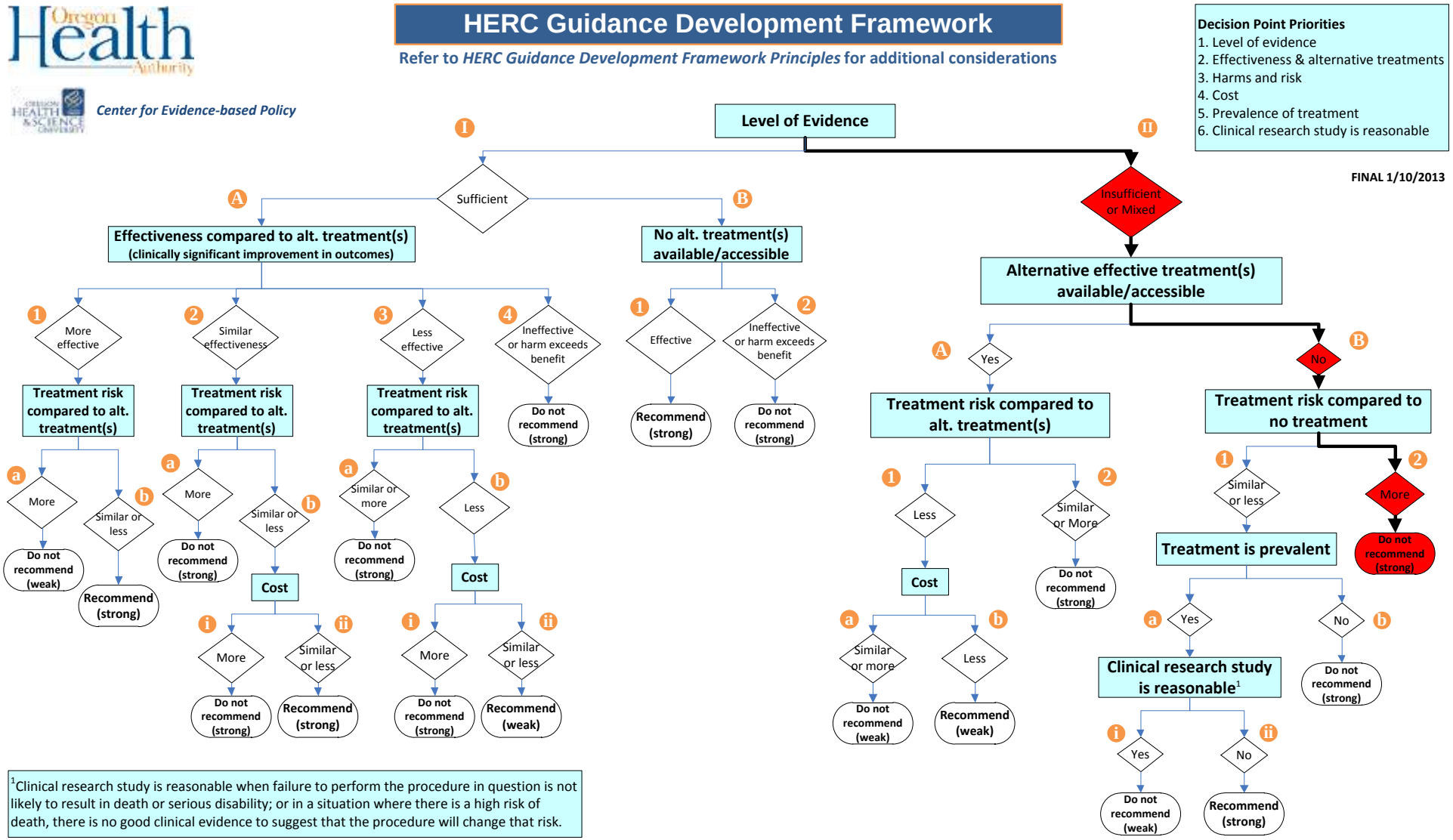
Appendix C. HERC Guidance Development Framework

Validated questionnaire to assess genetic risk in all pregnant women

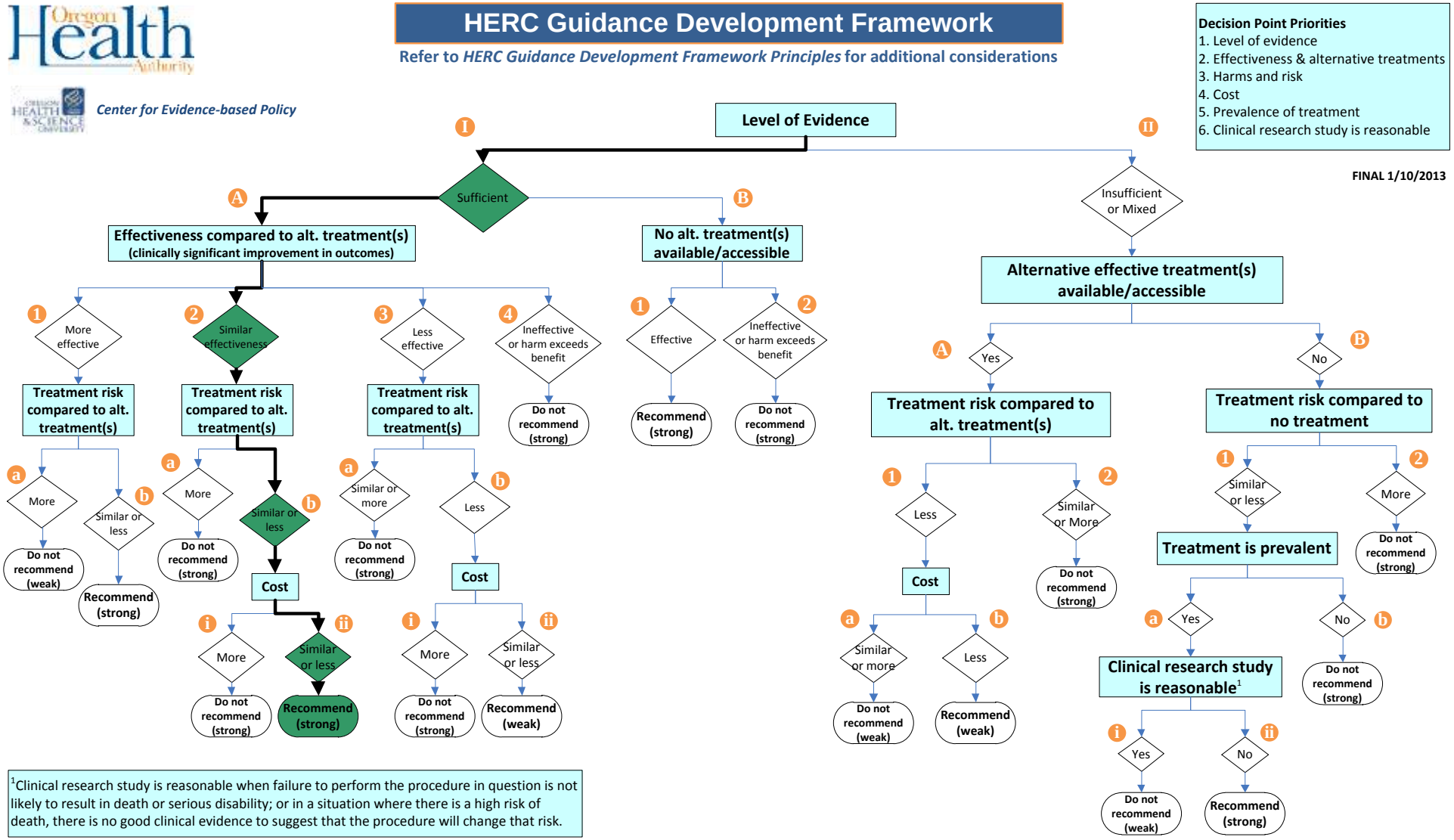


[1]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Screening for thrombophilia

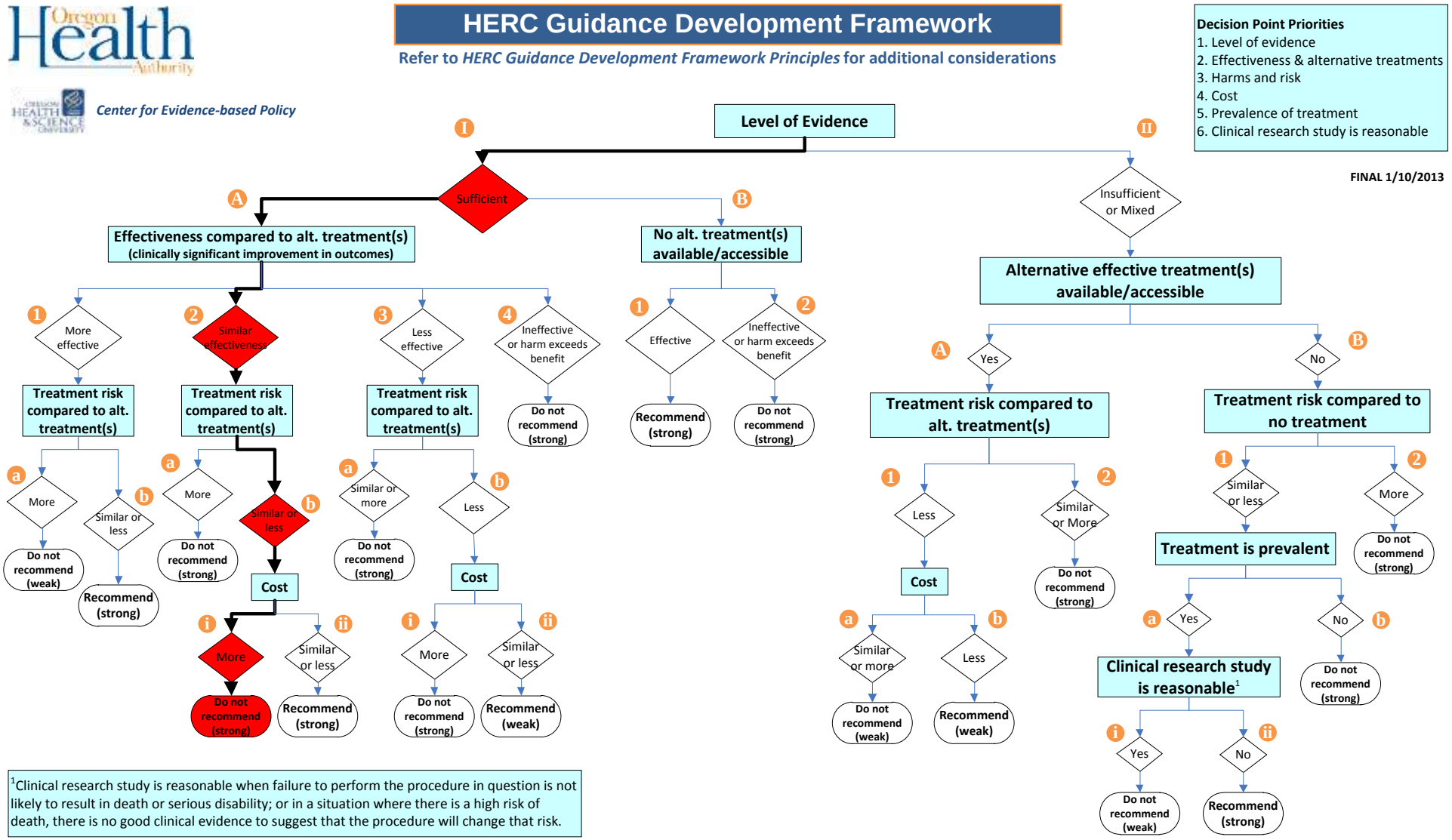


Array CGH testing when karyotype normal and structural anomaly on US; Screen high-risk ethnic groups for hemoglobinopathies; Aneuploidy screening in first or second trimester; CVS or amnio for + aneuploidy screen, maternal age > 34, fetal structural anomalies, + FH, elevated risk of neural tube defect or maternal request; Screening for Tay-Sachs carrier status using Hex A in high risk populations; Screening for CF carrier status; Screening for fragile X carrier status in women with +FH or risk factors; Screening of Ashkenazi Jewish population for specific genetic diseases; Expanded carrier screening



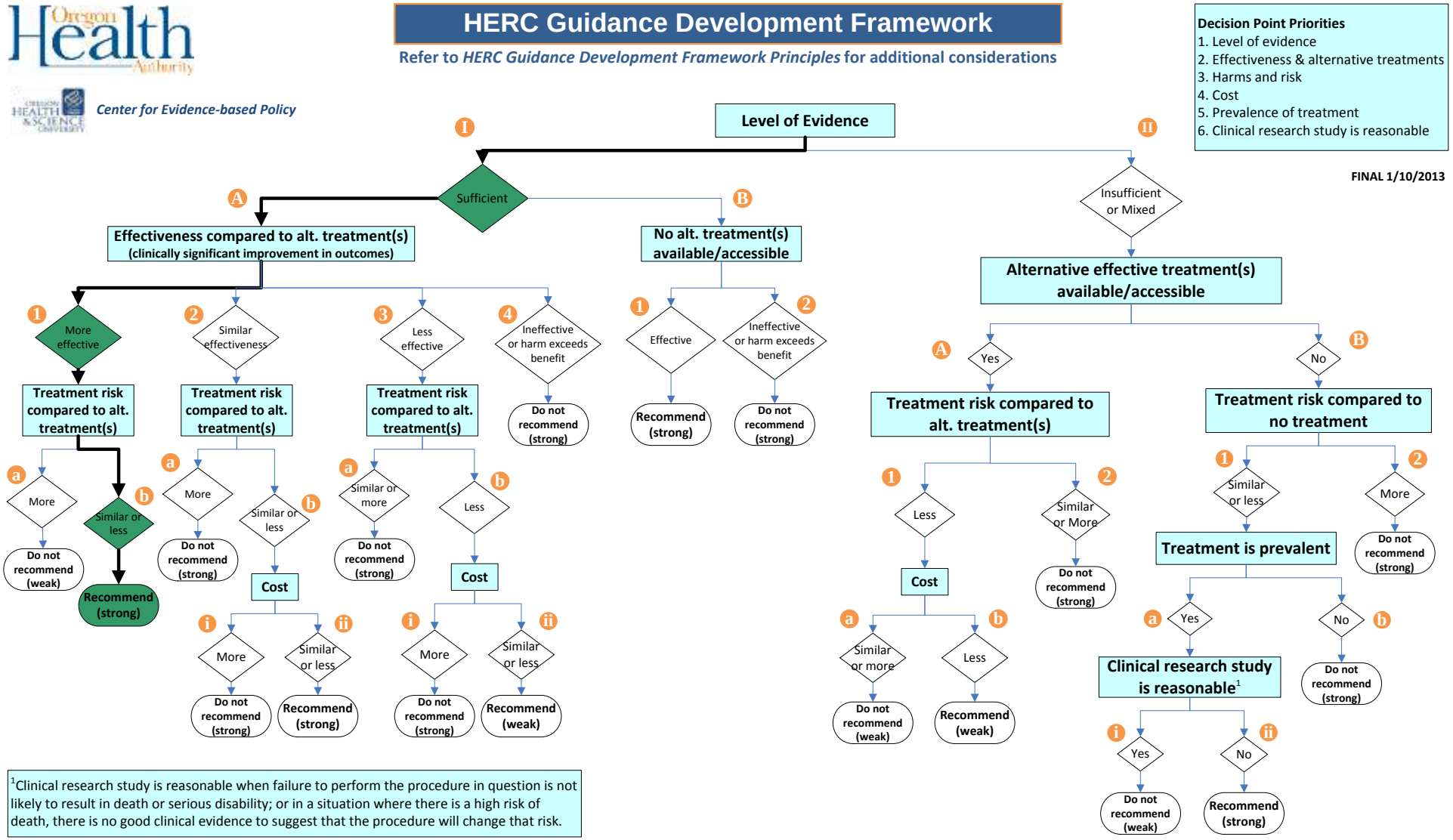
[1]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

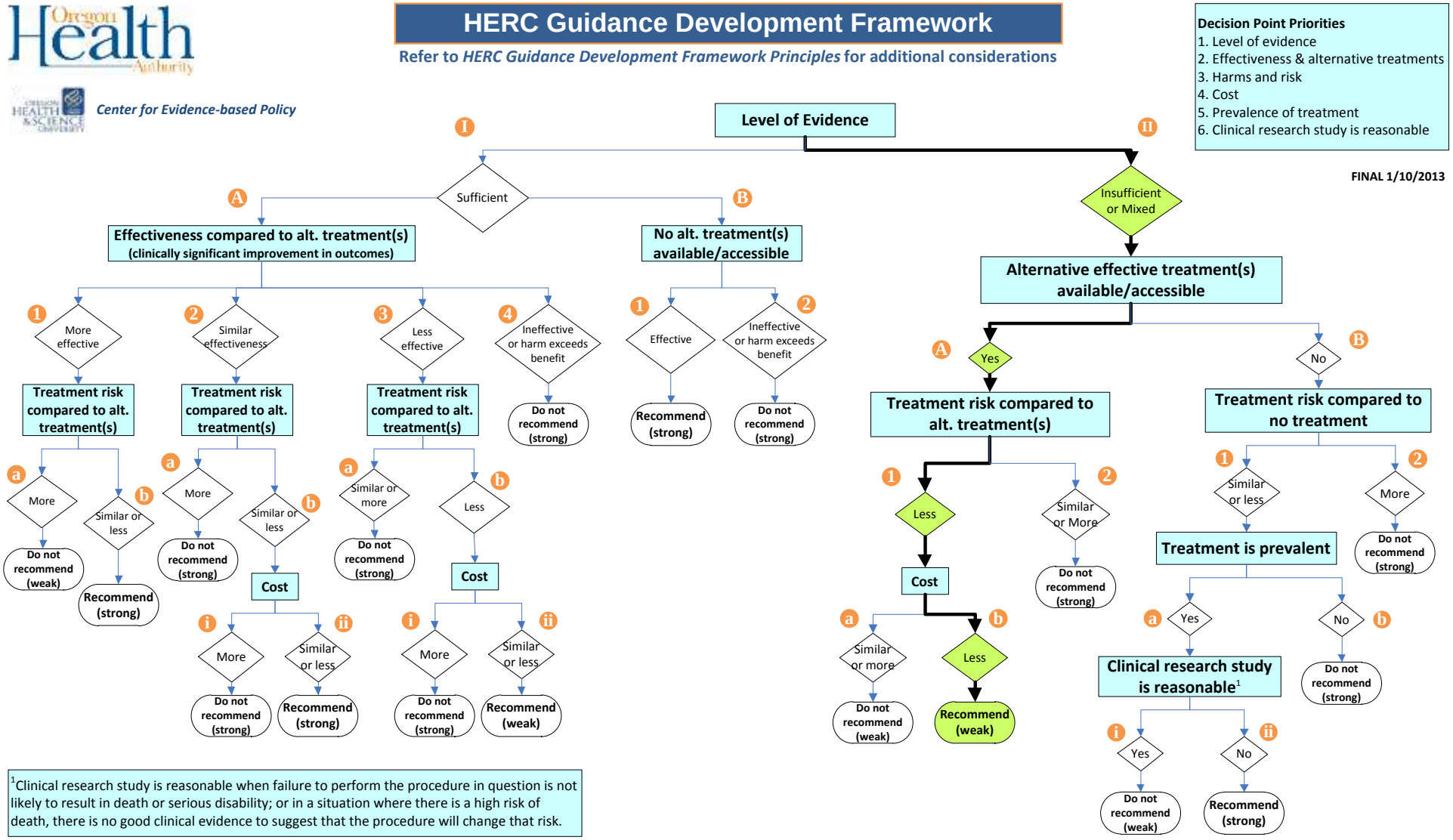
Aneuploidy testing with QF-PCR; Aneuploidy testing with FISH



[1]Clinical 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.

Cell free fetal DNA testing



[1]Clinical 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