

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE: PRENATAL GENETIC TESTING
DRAFT FOR 4/4/2013 EbGS MEETING MATERIALS

HERC COVERAGE GUIDANCE

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

- Pretest genetic counseling prior to CVS, amniocentesis, array CGH, and spinal muscular atrophy screening

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

- 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 18-20weeks 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 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, unexplained autism through the pregnant woman's maternal line
- Screening for spinal muscular atrophy once in a lifetime in high risk patients with pretest genetic counseling
- Screening those with Ashkenazi Jewish heritage additionally for Canavan disease, and familial dysautonomia
- Expanded carrier screening only for those genetic conditions previously identified with enough evidence or guidelines to support a weak recommendation for coverage

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
- Expanded carrier screening extending beyond the explicitly identified testing with evidence or guidelines to support a weak recommendation 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 (15 weeks 0 days</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 defects.</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)
	and 20 weeks 0 days).	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	<p>Provide information at first visit</p> <p>Offer if positive aneuploidy screening (details not provided)</p> <p>Offer if both parents are sickle cell or thalassemia carriers</p>	<p>Maternal request</p> <p>Offer CVS in first trimester if:</p> <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 <p>Offer amniocentesis if:</p> <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 	<p>Three different screening algorithms provided, with no recommendation for which to use</p> <p>Perform risk assessment using first trimester strategy (nuchal translucency, serum PAPP-A, patient age) and/or second trimester strategy (triple or quad screen)</p> <p>High, intermediate and low risk not specified, but examples given (1/50, 1/200)</p> <p>CVS or amniocentesis offered if screening suggests “high risk”, depending on gestational age</p>

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
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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 highly recommended prior to CVS/amniocentesis <i>(strong 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.	Not recommended for coverage <i>(weak recommendation)</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> Genetic counseling is highly recommended prior to testing <i>(strong 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.	<i>Array CGH is recommended for coverage for stillbirth >20 weeks gestation (based on expert opinion)</i>
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	Recommend for coverage in patients with a family history of unexplained mental retardation

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	or a history of fragile X mental retardation, premature ovarian failure, adult onset ataxia, unexplained autism through the pregnant woman's maternal line (<i>weak recommendation</i>)
Screening for thrombophilia	No benefit, no harm	Low	Limited	Limited	3 experts believe that the specific group of hx of fetal loss associated with evidence of placental ischemia and thrombosis and is controversial. No studies. It is done in practice (and are offered in next pregnancy). Experts recommend for those with fetal loss after 10 weeks with placental ischemia and thrombosis (placental pathology looked at).	Screening for thrombophilia is not recommended for coverage (<i>weak recommendation</i>)
Fetal genetic analysis of fetuses at risk for fetal skeletal dysplasia	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	<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
based on US					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.	
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 in high risk patients (<i>weak recommendation</i>) With pretest genetic counseling (<i>strong recommendation</i>)
Screening of Ashkenazi Jewish population for	Likely beneficial, minimal risks	Low	Moderate	Moderate variability	Conflicting recommendations on number of conditions to screen for. ACOG	Screening is recommended for coverage for those of Ashkenazi Jewish heritage for Tay-Sachs disease, Canavan

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
specific genetic diseases					recommends 4 and ACMG recommends 8 tests.	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 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	This incorporates screening for multiple carrier states, and as long as the clinician can select the specific 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)	Coverage is recommended for expanded carrier screening only for those genetic conditions previously identified with enough evidence or guidelines to support a weak recommendation for coverage (<i>weak recommendation</i>) Coverage is not recommended for an unlimited variety of tests offered as part of expanded carrier 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 C. HERC Guidance Development Framework

Validated questionnaire to assess genetic risk in all pregnant women

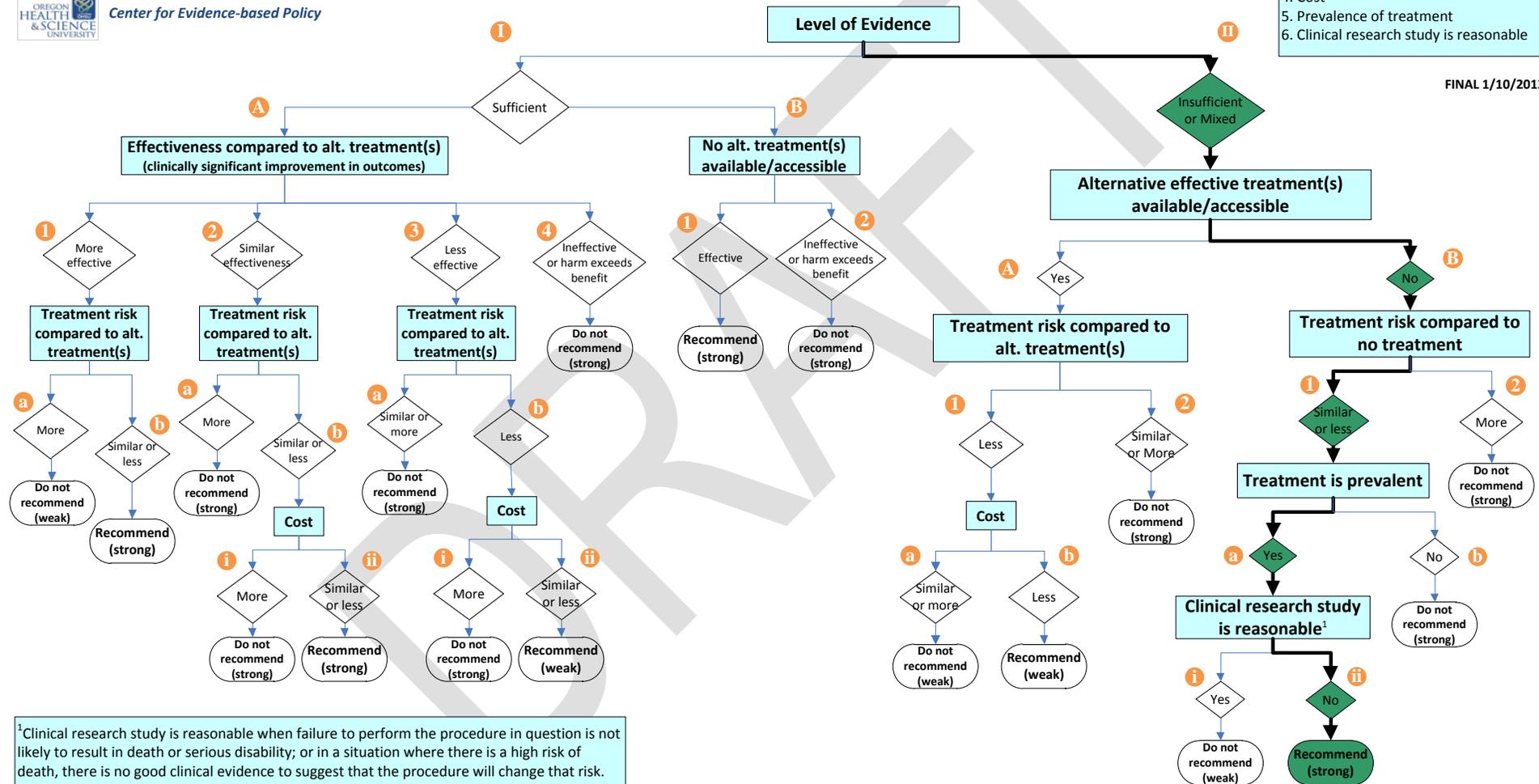


HERC Guidance Development Framework

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



Ultrasound for structural anomaly screen at 18-20 weeks; Screening for thrombophilia

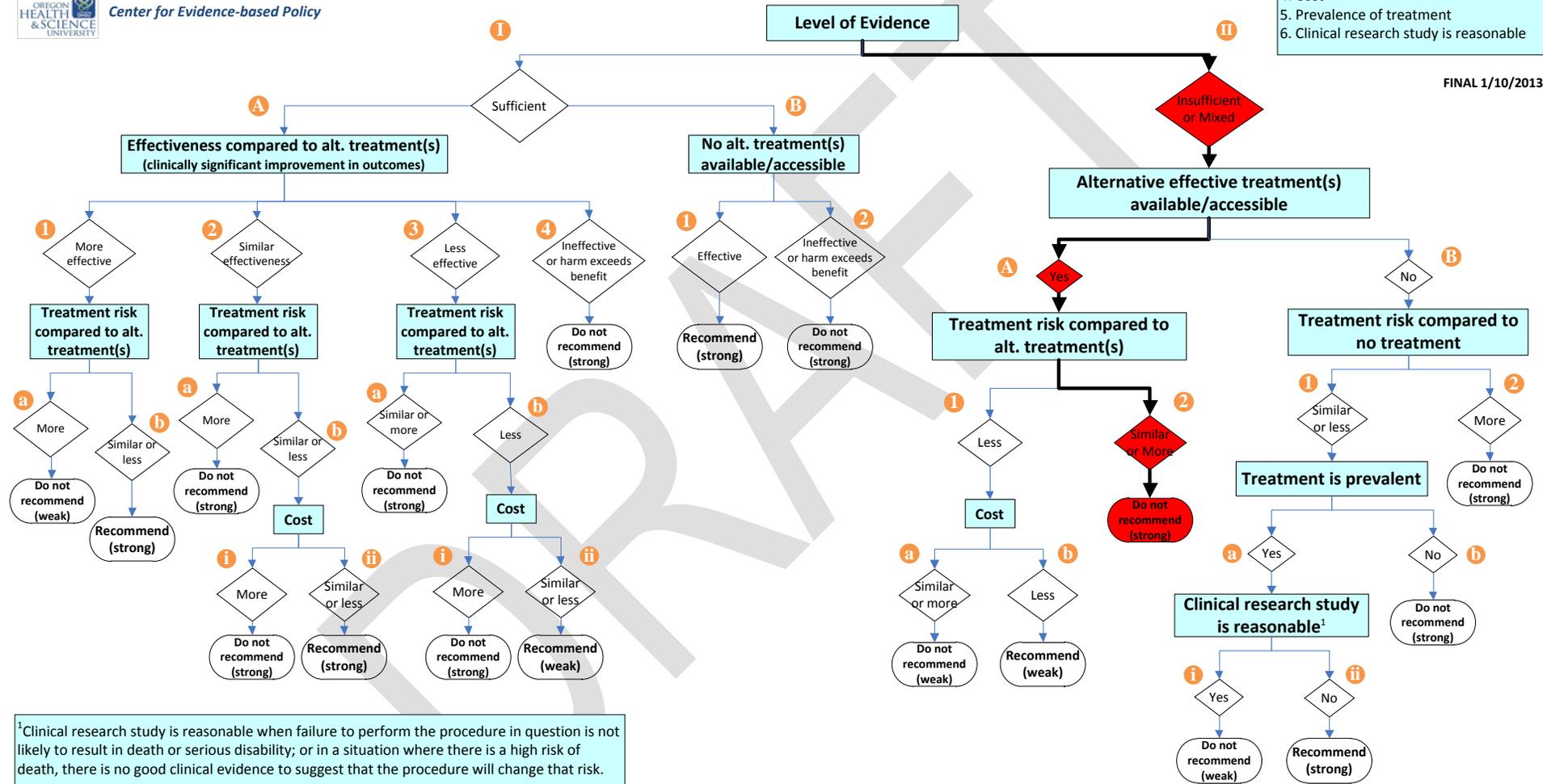


HERC Guidance Development Framework

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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



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



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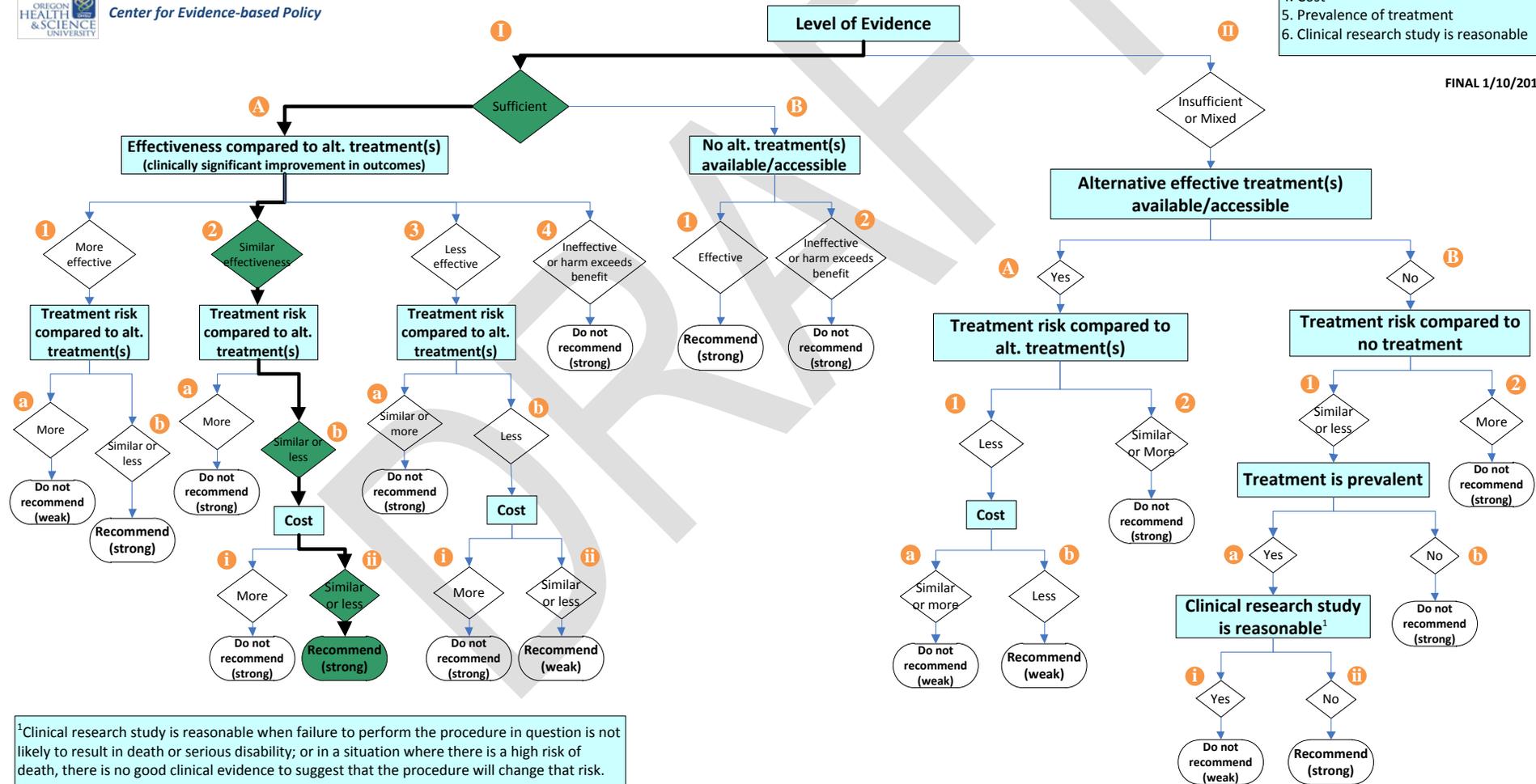
HERC Guidance Development Framework

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



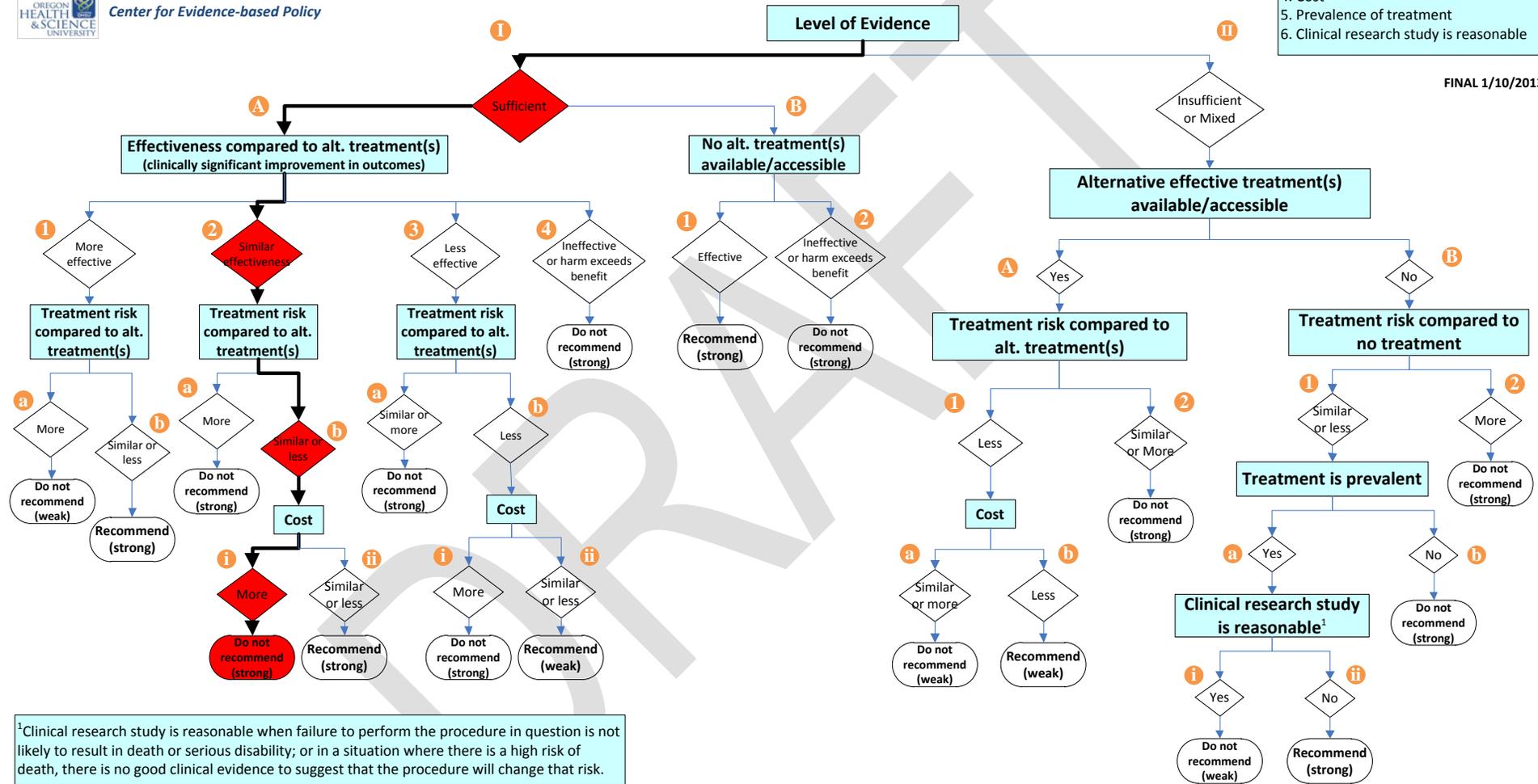
HERC Guidance Development Framework

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- Decision Point Priorities**

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 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



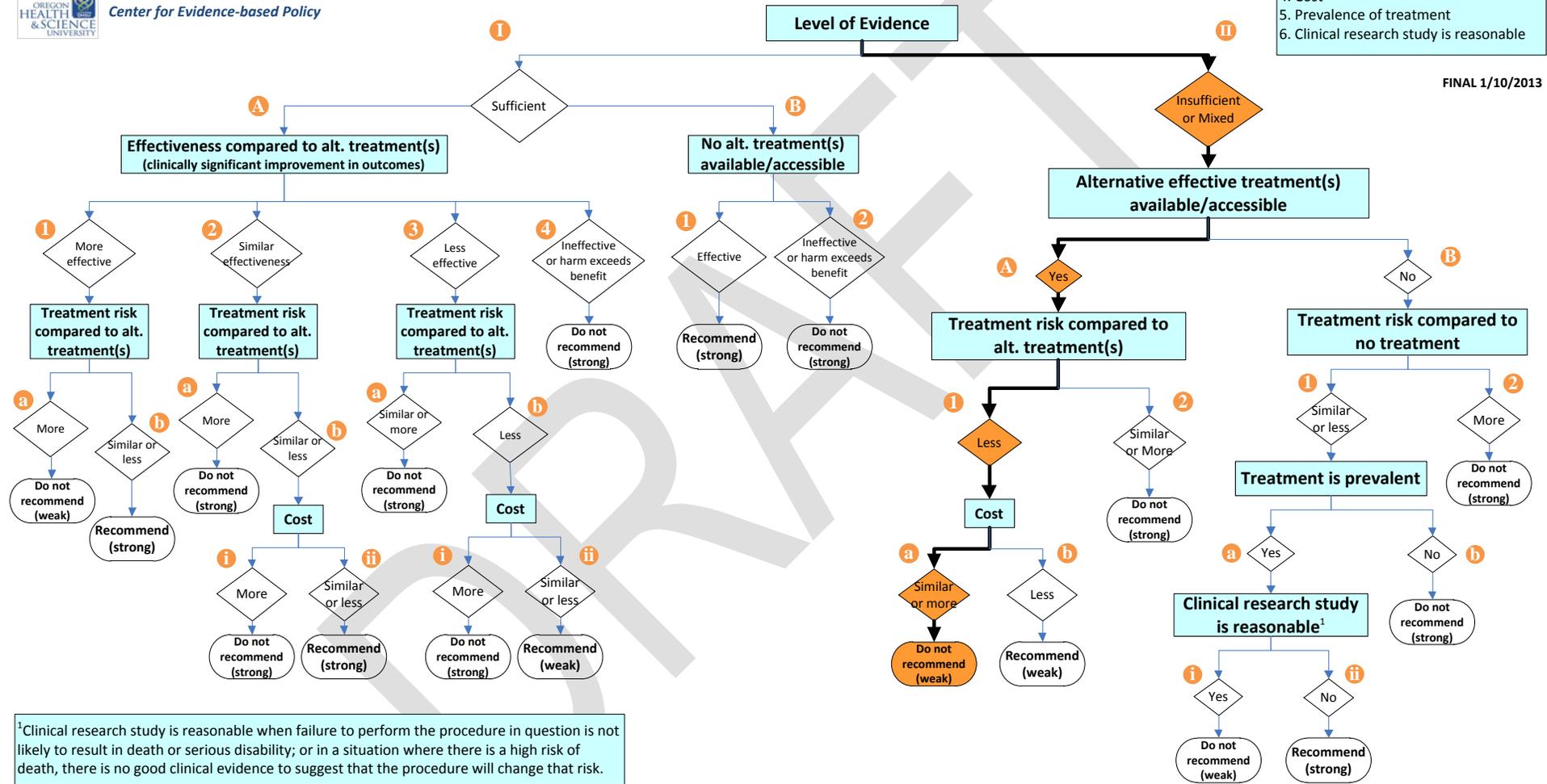
HERC Guidance Development Framework

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- Decision Point Priorities**

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

FINAL 1/10/2013



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

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