Master List of References

Glossary of Genetic Terms Used in This Review

List of Reviewers

Listing of Reviewers' Comments and Specific Responses

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Genetic Testing Glossary

ACMG – American College of Medical Genetics.

Advanced maternal age -- Women over age 34 (age 35 at delivery) at increased risk for nondisjunction trisomy in fetus.

Allele -- Alternative form of a genetic locus; a single allele for each locus is inherited from each parent (e.g., at a locus for eye color the allele might result in blue or brown eyes).

Amino acid -- Any of a class of 20 molecules that are combined to form proteins in living things. The sequence of amino acids in a protein and hence protein function are determined by the genetic code.

Amniocentesis -- Prenatal diagnosis method to obtain amniotic fluid for diagnostic purposes.

Amniocyte -- Cells in the amniotic fluid obtained by amniocentesis, used for determining the number and kind of chromosomes of the fetus and, when indicated, biochemical or DNA studies.

Amplification -- Any process which increases the number of copies of a specific DNA fragment; can be in vivo or in vitro.

Analyte -- The substance measured by a laboratory test; for instance, a specific mutation or allele.

Analytical performance – A term encompassing analytic sensitivity, analytic specificity, assay robustness and assay reliability.

Analytical sensitivity -- The probability that a test will detect an analyte, or a mutation or an alteration when it is present in a specimen. Usually expressed as a percentage.

Analytical specificity -- The probability that a test will be negative when an analyte, or a mutation or an alteration is absent from a specimen. Usually expressed as a percentage.

The following hypothetical example illustrates analytical sensitivity and specificity: Using DNA samples from 100 known carriers of mutation B for disease A, a PCR/restriction test detects this mutation in 92 of the samples. Thus, the analytical sensitivity is 92%, with 8 false negatives. In a parallel test using DNA samples from 100 known unaffected (no mutations, no family history) individuals, the same test detects mutations in 5 of the samples, in which it is known that there is no mutation. Thus, the analytical specificity is 95%, with 5 false positives.

Analytical validity -- The ability of a test to measure the property or characteristic that it was designed to measure (in the above example, specific mutations) by calculating such values as specificity and sensitivity.

Autosomal dominant -- A gene on one of the non-sex chromosomes that can be expressed, even if only one copy is present. The chance of passing the gene to offspring is 50% for each pregnancy.

Autosome -- A chromosome not involved in sex determination. The diploid human genome consists of a total of 46 chromosomes: 22 pairs of autosomes, and 1 pair of sex chromosomes (the X and Y chromosomes).

Base pair (bp) -- Two nitrogenous bases (adenine and thymine or guanine and cytosine) held together by weak bonds. Two strands of DNA are held together in the shape of a double helix by the bonds between base pairs.

Base sequence -- The order of nucleotide bases in a DNA molecule; determines structure of proteins encoded by that DNA.

Birth defect -- Any harmful trait, physical or biochemical, present at birth, whether the result of a genetic or non-genetic factor.

Buccal sample – Cells from inside the mouth that can be used for DNA testing, usually collected via mouthwash or scraping the cheek with a scoop, brush, or pad.

Candidate gene -- A gene located in a chromosome region suspected of being involved in a disease.

Carrier -- An individual who possesses a mutant allele but does not express it in the phenotype, either because of a dominant allelic partner or because the mutation is nonpenetrant.

Cell -- The basic unit of any living organism that carries on the biochemical processes of life.

CFTR – Cystic Fibrosis Transmembrane Regulator *(CFTR)*, the gene responsible for cystic fibrosis.

Chorionic villus sampling -- An invasive prenatal diagnostic procedure involving removal of villi from the human chorion to obtain chromosomes and cell products for diagnosis of disorders in the human embryo.

Chromosome -- In the eukaryotic nucleus, one of the threadlike structures consisting of chromatin which carries genetic information arranged in a linear sequence.

Clinical performance – A term encompassing clinical sensitivity, clinical specificity, penetrance and gene/environmental modifiers.

Clinical sensitivity -- The proportion of individuals with a specified clinical disorder whose test values indicate that the disorder is present (e.g. the mutation associated with the disorder is identified).

Clinical specificity The proportion of individuals who do not have a specified clinical disorder and whose test results indicate that the disorder is not present.

The following hypothetical example illustrates clinical sensitivity and specificity: A clinician determines that 100 patients have recessively inherited disease C, based on symptoms, family history, and ethnicity. Upon genetic testing, 60 of the patients are shown to have 2 mutations in gene D. Thus, the clinical sensitivity is 60%. The remaining 40 patients may have only one or no mutations in D. The same clinician sees 100 patients who

do not have disease C. When tested, 5 of the individuals are shown to have 2 mutations in D. Thus, the clinical specificity is 95%.

Clinical utility -- The value a test in diagnosing/ruling out a disease, in suggesting treatment or prevention strategies, and in evaluating risks and benefits associated with the test.

Clinical validity -- The ability of a test to distinguish affected and unaffected populations, including a determination of the probability of being affected. The clinical sensitivity, specificity, and predictive value of a test.

Clone -- A genetically engineered exact copy of biological material such as a DNA segment (e.g., a gene or other region), a whole cell, or a complete organism.

Cloning -- Using specialized DNA technology to produce multiple, exact copies of a single gene or other segment of DNA to obtain enough material for further study. This process, used by researchers in the Human Genome Project, is referred to as cloning DNA. The resulting cloned (copied) collections of DNA molecules are called clone libraries. A second type of cloning exploits the natural process of cell division to make many copies of an entire cell. The genetic makeup of these cloned cells, called a cell line, is identical to the original cell. A third type of cloning produces complete, genetically identical animals such as the famous Scottish sheep, Dolly.

Complex trait -- Trait that has a genetic component that does not follow strict Mendelian inheritance. May involve the interaction of two or more genes or gene-environment interactions.

Confidentiality -- In genetics, the expectation that genetic material and the information gained from testing that material will not be available without the donor's consent.

Confirmatory testing -- Repeat testing generally performed to corroborate a positive test result.

Congenital -- Any trait present at birth, whether the result of a genetic or non-genetic factor.

Contiguous genes -- Genes physically close on a chromosome that, when acting together, express a phenotype.

Cystic fibrosis -- An autosomal recessive genetic condition of the exocrine glands, which causes the body to produce excessively thick, sticky mucus that clogs the lungs and pancreas, interfering with breathing and digestion.

Cytogenetics -- The study of the physical appearance of chromosomes.

Deletion -- The loss of a segment of the genetic material from a chromosome; can lead to a disease or abnormality.

Diagnostic test -- A test performed to determine the presence or absence of a specific medical condition.

Disorder -- Any deviation from the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms and signs whose pathology and prognosis may be known or unknown.

DNA (deoxyribonucleic acid) -- The molecule that encodes genetic information. DNA is a double-stranded molecule held together by weak bonds between base pairs of nucleotides. The four nucleotides in DNA contain the bases adenine (A), guanine (G), cytosine (C), and thymine (T). In nature, base pairs form only between A and T and between G and C; thus the base sequence of each single strand can be deduced from that of its partner.

DNA bank -- A service that stores DNA extracted from blood samples or other human tissue.

DNA probe -- Any biochemical used to identify or isolate a gene, a gene product, or a protein.

DNA sequence -- The relative order of base pairs, whether in a DNA fragment, gene, chromosome, or an entire genome.

DNA sequencing -- In the "plus and minus" or "primed synthesis" method, DNA is synthesized in vitro in such a way that it is radioactively labeled and the reaction terminates specifically at the position corresponding to a given base; in the "chemical" method, single stranded DNA is subjected to several chemical cleavage protocols that selectively make breaks on one side of a particular base.

Dominant -- An allele that is almost always expressed, even if only one copy is present.

Electrophoresis -- A method of separating large molecules (such as DNA fragments or proteins) from a mixture of similar molecules. An electric current is passed through a medium containing the mixture, and each kind of molecule travels through the medium at a different rate, depending on its electrical charge and size. Agarose and acrylamide gels are the media commonly used for electrophoresis of proteins and nucleic acids.

ELSI -- Ethical, legal and social implications (of Human Genome Project).

Equivocal result -- A test result that cannot be interpreted as either negative or positive.

Ethics -- The study of fundamental principles which defines values and determines moral duty and obligation.

Eugenics -- The study of improving a species by artificial selection; usually refers to the selective breeding of humans.

Exon -- The protein-coding DNA sequence of a gene.

Expected results -- Known outcomes for a specific test for a particular disease or condition, obtained from published data, reports, etc.

False negative -- Does have the abnormality or disease and is incorrectly classified by the test.

False positive -- Does not have the abnormality or disease and is incorrectly classified by the test.

Fluorescence in situ hybridization (FISH) -- A physical mapping approach that uses fluorescein tags to detect hybridization of probes with metaphase chromosomes and with the less-condensed somatic interphase chromatin.

Gene -- A hereditary unit that occupies a certain position on a chromosome; a unit that has one or more specific effects on the phenotype, and can mutate to various allelic forms. The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule).

Gene amplification -- Any process by which specific DNA sequences are replicated disproportionately greater than their representation in the parent molecules; during development, some genes become amplified in specific tissues. Repeated copying of a piece of DNA; a characteristic of tumor cells.

Gene product -- The biochemical material, either RNA or protein, resulting from expression of a gene. The amount of gene product is used to measure how active a gene is; abnormal amounts can be correlated with disease-causing alleles.

Gene therapy -- An experimental procedure aimed at replacing, manipulating, or supplementing nonfunctioning or misfunctioning genes with healthy genes.

Gene transfer -- Incorporation of new DNA into and organism's cells, usually by a vector such as a modified virus. Used in gene therapy.

Genetic code -- The sequence of nucleotides, coded in triplets (codons) along the mRNA, that determines the sequence of amino acids in protein synthesis. A gene's DNA sequence can be used to predict the mRNA sequence, and the genetic code can in turn be used to predict the amino acid sequence.

Genetic counseling -- The educational process that helps individuals, couples, or families to understand genetic information and issues that may have an impact on them.

Genetic discrimination -- Prejudice against those who have or are likely to develop an inherited disorder.

Genetic engineering -- Altering the genetic material of cells or organisms to enable them to make new substances or perform new functions.

Genetic marker -- A gene or other identifiable portion of DNA whose inheritance can be followed.

Genetic modifiers – Other genes that can influence the phenotype associated with the gene of interest.

Genetic polymorphism -- Difference in DNA sequence among individuals, groups, or populations (e.g., genes for blue eyes versus brown eyes).

Genetic predisposition -- A genotype that increases the risk but is insufficient to result in disease. Impaired expression of alleles at other gene loci and/or environmental factors are needed before disease appears.

Genetic screening -- Testing a group of people to identify individuals at high risk of having or passing on a specific genetic disorder.

Genetic testing -- Analyzing an individual's genetic material to determine predisposition to a particular health condition or to confirm a diagnosis of genetic disease.

Genetic variation -- A phenotypic variability of a trait in a population attributed to genetic heterogeneity.

Genetics -- The study of inheritance patterns of specific traits.

Genome -- All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genome project -- Research and technology-development effort aimed at mapping and sequencing the genome of human beings and certain model organisms.

Genotype -- 1) The genetic constitution of an organism, either overall or at a specific locus, as distinguished from its physical appearance (its phenotype). 2) The specific allelic composition of a gene, or set of genes, established at DNA level.

Hardy-Weinberg Law -- The concept that both gene frequencies and genotype frequencies will remain constant from generation to generation in an infinitely large, interbreeding population in which mating is at random and there is no selection, migration or mutation.

Heterozygote -- Having two alleles on homologous chromosomes that are different for a given gene.

Homozygote -- Having two alleles on homologous chromosomes that are identical for a given gene.

Human Genome Project -- Collective name for several projects begun in 1986 by the Department of Energy (DOE) to create an ordered set of DNA segments from known chromosomal locations, develop new computational methods for analyzing genetic map and DNA sequence data, and develop new techniques and instruments for detecting and analyzing DNA. This DOE initiative is now known as the Human Genome Program. The joint national effort, led by DOE and NIH, is known as the Human Genome Project.

Hybridization -- The pairing of a single-stranded, labeled probe (usually DNA) to its complementary sequence.

In situ hybridization -- The pairing of a labeled probe to its complementary sequence within intact, banded chromosomes.

In vitro -- Studies performed outside a living organism such as in a laboratory.

In vivo -- Studies carried out using living organisms.

Incidence -- Number or proportion of new cases of a specified condition in a population over a specified time period.

Incomplete penetrance -- The gene for a condition is present, but not obviously expressed, in all individuals with the gene in a family.

Informed consent -- An individual willingly agrees to participate in an activity after first being advised of the risks and benefits.

Inherit -- In genetics, to receive genetic material from parents through biological processes.

Intellectual property rights -- Patents, copyrights, and trademarks.

Karyotype -- A set of photographed, banded chromosomes arranged in order from largest to smallest in a standard format showing the number, size, and shape of each chromosome type; used in low-resolution physical mapping to correlate gross chromosomal abnormalities with the characteristics of specific diseases.

Kilobase (kb) -- Unit of length for DNA fragments equal to 1000 nucleotides.

Locus (pl. loci) The position on a chromosome of a gene or other chromosome marker; also, the DNA at that position. The use of locus is sometimes restricted to mean expressed DNA regions.

Lysate -- a liquid containing the components of disrupted cells that is used as the source of DNA for testing patient samples.

Masked (blind) testing -- Use of a specimen whose contents are unknown to the laboratory, or to the laboratory technician, to assess the ability of the laboratory to perform a test correctly.

Megabase (Mb) -- Unit of length for DNA fragments equal to 1 million nucleotides.

Mendelian inheritance -- One method in which genetic traits are passed from parents to offspring. Named for Gregor Mendel, who first studied and recognized the existence of genes and this method of inheritance.

Modeling -- The use of statistical analysis, computer analysis, or model organisms to predict outcomes of research.

Molecular biology -- The study of the structure, function, and makeup of biologically important molecules.

Molecular genetics -- The study of macromolecules important in biological inheritance.

Monogenic disorder -- A disorder caused by mutation of a single gene.

Multifactorial -- A characteristic influenced in its expression by many factors, both genetic and environmental.

Mutation -- Any heritable change in DNA sequence. A process by which genes undergo a structural change.

Negative predictive value -- The probability that a subject with a negative test result actually does not have the disease. Note: This is an a posteriori (or post-test) probability.

Northern blot -- A gel-based laboratory procedure that locates mRNA sequences on a gel that are complementary to a piece of DNA used as a probe.

Nucleus -- The cellular organelle in eukaryotes that contains most of the genetic material.

Oligonucleotide -- A molecule usually composed of 25 or fewer nucleotides; used as a DNA synthesis primer.

Patent -- In genetics, conferring the right or title to genes, gene variations, or identifiable portions of sequenced genetic material to an individual or organization.

PCR -- See polymerase chain reaction.

Pedigree -- A family tree diagram that shows how a particular genetic trait or disease has been inherited through many generations of a family.

Penetrance -- The frequency with which a genotype manifests itself in a specific phenotype; the proportion of individuals who manifest that genotype at the phenotypic level. For example, if 100 females have two D mutations and 70 have symptoms of the disorder, the penetrance is 70%.

Phenotype -- The biochemical, physiological and physical characteristics of an individual, as determined by the genotype and the environment in which it is expressed; also, in a more limited sense, the expression of some particular gene or genes.

Polymerase -- Any enzyme that catalyzes the formation of DNA or RNA from deoxyribonucleotides or ribonucleotides.

Polymerase chain reaction (PCR) -- A method for amplifying a DNA base sequence using a heat-stable polymerase and two 20-base primers, one complementary to the (+) strand at one end of the sequence to be amplified and one complementary to the (-) strand at the other end. Because the newly synthesized DNA strands can subsequently serve as additional templates for the same primer sequences, successive rounds of primer annealing, strand elongation, and dissociation produce rapid and highly specific amplification of the desired sequence. PCR also can be used to detect the existence of the defined sequence in a DNA sample.

Polymorphism -- Frequently occurring (common), usually normal variation, in a defined nucleotide sequence. Polymorphisms in genes may result in protein polymorphisms. A protein polymorphism is said to occur when the most common allele has a frequency of no greater than 99%.

Positive predictive value -- The probability that an individual with a positive test has, or will develop, a particular disease, or characteristic, that the test is designed to detect.

Post-analytical – that phase of laboratory testing occurring after the test result has been generated (e.g., test interpretation, test reporting, and consultation).

Pre-analytical – That phase of laboratory testing occurring before the test has been run (e.g., test requisition information, sample suitability, and sample labelling/handling.

Presymptomatic testing -- A test for a genetic disease before it becomes apparent but which may develop if affected by certain factors.

Prevalence -- The proportion of individuals in a population having a disease.

Primer -- Short preexisting polynucleotide chain to which new deoxyribonucleotides can be added by DNA polymerase.

Privacy -- In genetics, the right of people to restrict access to their genetic information.

Probability The long term frequency of an event relative to all alternative events, and usually expressed as decimal fraction.

Proband -- Individual in a family who brought the family to medical attention.

Probe -- Single-stranded DNA or RNA molecules of specific base sequence, labeled either radioactively or immunologically, that are used to detect the complementary base sequence by hybridization.

Proficiency testing (PT) -- The use of masked (blind) testing to assess whether a lab can perform a test correctly. Usually, the samples are provided by an organization independent of the laboratories performing the test. Also, a program in which specimens are periodically sent to participating laboratories for analysis and/or identification; in which the results of each laboratory are compared with those of other participants and/or a target result. The results are then reported to participating laboratories and, possibly, others.

Prognosis -- Prediction of the course and probable outcome of a disease.

Protein -- A large molecule composed of one or more chains of amino acids in a specific order; the order is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs; and each protein has unique functions. Examples are hormones, enzymes, and antibodies.

Public policy -- A set of action guidelines or rules that results from the actions or lack of actions of governmental entities.

Quality assurance -- A laboratory program that ensures creation of reproducible results that are clinically useful to patients and providers, in a timely fashion, through minimization of human error.

Quality control -- A substance, sample or procedure intended to verify performance characteristics of a system.

Recessive gene -- A gene which will be expressed only if there are 2 identical copies or, for a male, if 1 copy is present on the X chromosome.

Recombinant DNA technology -- Procedure used to join together DNA segments in a cell-free system (an environment outside a cell or organism). Under appropriate conditions, a recombinant DNA molecule can enter a cell and replicate there, either autonomously or after it has become integrated into a cellular chromosome.

Reference material -- Material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for calibration of a measuring system, the assessment of a measurement procedure, or for assigning values to materials

Reference method -- A thoroughly investigated method, in which exact and clear descriptions of the necessary conditions and procedures are given for the accurate determination of one or more property values; the documented accuracy and precision of the method are commensurate with the method's use for assessing the accuracy of other methods for measuring the same property values or for assigning reference method values to reference materials.

Reproducibility -- The closeness of the agreement between the results of measurements of the same analyte, where the measurements are carried out under changed conditions.

Note: a) Changed conditions may include: principle or method of measurement, observer measuring instrument, location, conditions of use, and time; b) Reproducibility may be expressed quantitatively in terms of dispersion characteristics of the results. For example, using samples from 5 individuals known to be homozygous for the disease F caused by mutation G, 2 technicians using 3 different sequencers on 5 different days can detect the presence of the mutation in all 5 samples in every case, so the reproducibility is 100%.

Residual risk – Another name for the negative predictive value. The risk of the disorder in an individual (or couple) with a negative test result.

Restriction fragment length polymorphism (RFLP) -- Variation between individuals in DNA fragment sizes cut by specific restriction enzymes; polymorphic sequences that result in RFLPs are used as markers on both physical maps and genetic linkage maps. RFLPs usually are caused by a mutation at a cutting site.

Risk communication -- In genetics, a process in which a genetic counselor or other medical professional interprets genetic test results and advises patients of the consequences for them and their offspring.

Screening test -- A test designed to identify subjects who are at sufficient risk of a specific disorder to benefit from further investigation or preventive action, among those who have not sought medical attention on account of symptoms of that disorder.

Sensitivity -- The proportion of individuals with the abnormality or disease that will have a positive test.

Sequence tagged site (STS) -- Short (200 to 500 base pairs) DNA sequence that has a single occurrence in the human genome and whose location and base sequence are known. Detectable by polymerase chain reaction, STSs are useful for localizing and orienting the mapping and sequence data reported from many different laboratories and serve as landmarks

on the developing physical map of the human genome. Expressed sequence tags (ESTs) are STSs derived from cDNAs.

Single nucleotide polymorphism (SNP) -- DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered.

Single gene disorder -- Hereditary disorder caused by a mutant allele of a single gene (e.g., Duchenne muscular dystrophy, retinoblastoma, sickle cell disease).

Southern blotting -- Transfer by absorption of DNA fragments separated in electrophoretic gels to membrane filters for detection of specific base sequences by radio-labeled complementary probes.

Specificity -- The proportion of individuals without the abnormality or disease that will have a negative test.

Syndrome -- The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease.

Tandem repeat sequences -- Multiple copies of the same base sequence on a chromosome; used as markers in physical mapping.

Technology transfer -- The process of transferring scientific findings from research laboratories to the commercial sector.

Trait -- Any detectable phenotypic property of an organism.

True negative -- Does not have the abnormality or disease and is correctly classified by the test.

True positive -- Does have the abnormality or disease and is correctly classified by the test.

Validation -- The action (or process) of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended result (can be performed at both analytical and clinical level).

Verification -- Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

VNTR -- Variable number tandem repeats; any gene whose alleles contain different numbers of tandemly repeated oligonucleotide sequences.

Western blot -- A technique used to identify and locate proteins, based on their ability to bind to specific antibodies.

Wild type -- The form of an organism that occurs most frequently in nature.

Many of these definitions have been taken from other sources including:

- Food and Drug Administration proposed "Instructions for Completing the Premarket Review Template for In-House Developed Genetic Tests; Draft Guidance for Clinical Laboratories and FDA Reviewers
- NCCLS MMIA standard: Molecular Diagnostic Methods for Genetic Diseases;
- Approved Guideline, the Interim Principles of the Task Force on Genetic testing (http://www.med.jhu.edu/tfgtelsi/principles.html,
- International Standard Organization/Technical Committee [ISO/TC] August 2000 definitions document, National Human Genome Research Institute (NHGRI
- The Genetics Education Center, University of Kansas Medical Center (http://www.kumc.edu/gec/glossnew.html)
- Oak Ridge National Laboratory - Human Genome Project Information (http://www.ornl.gov/TechResources/Human_Genome/glossary/glossary.html)

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