Australian Government
Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

CLINICAL UTILITY CARD FOR HERITABLE MUTATIONS WHICH INCREASE RISK IN [DISEASE AREA]

GLOSSARY

Introduction

The Medical Services Advisory Committee (MSAC) is developing a clinical utility card (CUC) format to help streamline the assessment of the utility of germline genetic testing for broad disease areas, such as cancer, cardiovascular or mental illness. As part of this approach, the need for a brief glossary of relevant terms became apparent. The following glossary is intended to referred to when completing a CUC or associated application.

Comments on this glossary are welcome, including on the terms identified or omitted, and on definitions adopted. These should be provided to:

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Actionable pathology test see clinically actionable

Affected individual
An individual diagnosed with the primary disease and who has symptoms of the primary disease, but who may or may not have a relevant germline mutation.

Analytical concordance
A comparison of the results of different tests using the same specimen.

Analytical reproducibility
A comparison of the results of the same test run multiple times on the same specimen.

Analytical validity
A comparison of the results of different tests against those of an accepted reference standard.

Cascade testing
Testing of family members of a proband for the identified germline mutation.

Clinical genome-wide sequencing
A generic term for the process used to determine the sequence of most, if not all, clinically significant genes and its associated interpretation, including bioinformatic analysis and clinical genotype–phenotype correlation. This approach would be undertaken by an appropriately certified laboratory to address a clinical question.

Clinical validity
An assessment of whether the different results of a test predict variations in the risk of future manifestations of the disease.

Clinical utility
Evidence that test results change patient management and improve health outcomes.

Clinically actionable
A pathology test result that may change patient management to improve health outcomes.

Diagnostic genetic testing (compare with predictive genetic testing)
Genetic testing that is applied to an affected individual in order to identify one or more mutations known to predict an increased risk of future manifestations of the disease compared with individuals with the disease who do not have such a mutation.

Exome
The subset of the genome which comprises all of the exons only (~1% of the genome).

Exon
The part of a gene that codes for a protein.

Expression
The variety of phenotypes associated with the presence of variation in a specific gene (genotype).

Familial

Relating to or occurring in a family or its members (a term generally preferred over "hereditary" because it captures a shared environment as well as shared genes).

Genetic heterogeneity

The occurrence of similar or identical phenotypes as a result of disruption of different genes.

Genome

The sum of all approximately ~20,000 human genes encoded in 46 chromosomes, together with non-coding variants.

Genotype

Specific genetic variants in an individual which are relevant for the disorder being considered.

Germline

Mutations which occur in the germ cells (eggs and sperm) and are heritable.

Incidental finding

Genetic variant(s) identified by testing unrelated to the primary disease.

Index case (see proband)

Inter-rater reliability

A comparison of the results of multiple assays with the same test and different interpreters and/or laboratories using the same specimen.

Monogenic (Mendelian) condition

A genetic condition resulting from altered function of a single gene in a given family.

Multifactorial inheritance

Non-monogenic inheritance of specific traits that are determined by the combined action of multiple genetic and environmental factors.

Multi-gene panel sequencing

The targeted sequencing, primarily by NGS, of a selection of genes associated with the primary disease.

Next generation sequencing (NGS)

Massively parallel sequencing technologies that produce many hundreds of thousands or millions of reads simultaneously.

Obligate carrier

An individual who may be clinically unaffected but who must carry a relevant germline mutation based on analysis of the family history.

Penetrance

The frequency with which a heritable trait is manifested by individuals carrying the principal gene or genes conditioning it.

Phenome

The constellation of relevant physical, chemical, pathological and biochemical traits of an individual which can change in response to genetic mutation and the environment, which are interpreted by a clinical expert, together with relevant personal medical and family history and other measurements, to make the judgment that the likelihood of finding a pathogenic germline mutation is ≥10%.

Phenotype

Outward physical manifestation of the genotype of an organism.

Predictive genetic testing (compare with diagnostic genetic testing)

Genetic testing that is applied to the biologically related family members of the subset of affected individuals who are shown to have a hereditary mutation in order to determine whether that mutation, known to predict an increased risk of manifesting the disease, is present.

Primary disease

The constellation of clinical features that raises the possibility of a relevant germline mutation and thus predisposition testing.

Primary finding

Genetic variant(s) identified by predisposition testing that explain the primary disease.

Primary genetic target (see star performer)

Proband

Individual (index case) in a family who is affected with the disease and has a relevant known germline mutation.

Secondary genetic target (see also primary genetic target)

The clinically actionable gene(s) for which sufficient evidence of clinical validity and clinical utility (albeit of a less rigorous standard than for star performers) justifies their inclusion in a set of options for concurrent diagnostic genetic testing of affected individuals being tested for star performers.

Somatic

Mutations that occur after conception, and are neither inherited nor passed on to offspring.

Star performer

The clinically actionable gene(s) for which the strongest clinical utility and/or cost-effectiveness argument is likely to apply for an affected individual.

Whole-exome sequencing (WES)

A process used to determine the DNA sequence of most of the protein-encoding exons found in the genome of an individual.

Whole-genome sequencing (WGS)

A process used to determine the sequence of most of the DNA content encompassing the entire genome of an individual.