orphanet

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Glossary and representation of terms related to diagnostic tests

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I. Purpose of the document

Orphanet offers a directory of diagnostic tests intended to help professionals to obtain a timely and accurate diagnosis for the patients affected by a rare disease (for more information, please refer to the “Data Collection and update of diagnostic tests” procedure, soon available).

Every diagnostic test in Orphanet is tagged, at least, with one **technical procedure** and one **purpose**.

The **technical procedure** is defined with a three level representation, if applicable: specialty, objective and technique:

- *Specialty*: Main method category (e.g.: Molecular genetics)

- *Objective*: Goal of the test (e.g.: Targeted mutation analysis)

- *Technique*: Specific technology used to reach the goal (e.g.: Sanger sequencing)

The **purpose** is the context in which the test is performed (e.g.: postnatal diagnostic).

This document shows the possible combinations of technical procedures that can be linked to a diagnostic test in Orphanet. It also contains glossary of all terms used for technical procedures and purposes.

II. Technical procedure representation

1. MOLECULAR GENETICS:

- Targeted mutation analysis
  - Sanger sequencing
  - NGS sequencing (except WES)
  - PCR based techniques
  - MLPA based techniques
- Mutation scanning / screening and sequence analysis of selected exons
  - Sanger sequencing
  - NGS sequencing (except WES)
  - PCR based techniques
- Sequence analysis: entire coding region
  - Sanger sequencing
  - NGS sequencing (except WES)
  - Whole exome sequencing (WES)
- Uniparental disomy study
  - Array based techniques
  - Microsatellite analysis
- Methylation analysis
  - MLPA based techniques
  - BS-Pyrosequencing
  - Array based techniques
- Deletion / duplication analysis
  - MLPA based techniques
  - PCR based techniques
  - Array based techniques
  - NGS sequencing (except WES)

2. CYTOGENETICS

- Detection of chromosome alterations large in size
  - FISH
  - M-FISH / SKY
  - Karyotyping
  - NGS sequencing (except WES)

- Detection of microdeletion / microduplication
  - MLPA based techniques
  - Array based techniques
  - FISH

- Chromosomal instability
  - Chromosome breakage study

3. BIOCHEMICAL GENETICS

- Analyte / enzyme assay

- Protein expression
  - Immunohistochemistry
  - Western blot

4. PARASITOLOGY
5. BACTERIOLOGY
6. VIROLOGY
7. MYCOLOGY
8. IMMUNOLOGY
9. HEMATOLOGY
10. PATHOLOGY
11. IMAGING
12. OTHER

III. Glossary

1. Specialties:

Molecular genetics: Set of procedures to study the structure and function of genes at a molecular level.

Cytogenetics: Set of procedures to study the structure and function of the chromosomes.

Biochemical genetics: Set of procedures to study the fundamental relationships between genes, protein, and metabolism.

Pathology: Set of procedures to perform macroscopic and pathological analysis.

Immunology: Set of procedures to assess the function or expression of antibodies.

Parasitology: Set of procedures applied to the identification of parasites.

Bacteriology: Set of procedures applied to the identification bacterial pathogens.

Virology: Set of procedures applied to the identification of virus.

Mycology: Set of procedures applied to the identification of fungi.

Hematology: Set of procedures applied to the identification of constitutional or somatic blood disorders.

Imaging: Technique of creating visual representations of the interior of a body for clinical analysis and medical intervention.

2. Objectives:

Targeted mutation analysis: Molecular genetics procedure for either a nucleotide repeat expansion (e.g., the trinucleotide repeat expansion associated with Huntington disease), or one or more specific mutations (e.g., Glu6Val for sickle cell anemia, a panel of mutations for cystic fibrosis).

Mutation scanning / screening and sequence analysis of selected exons: Molecular genetics procedure by which a segment of DNA is screened to identify known variant gene regions, and by which specific exons, likely to contain the disease-causing mutations, are sequenced to identify known or *de novo* sequence variations.

Sequence analysis: entire coding region: Molecular genetics procedure by which the nucleotide sequence is determined for the entire coding region of a gene to identify known or *de novo* sequence variations.

Uniparental disomy study: Molecular genetics procedure used to identify if specific chromosomes or chromosomal segments are maternally or paternally derived.

Methylation analysis: Molecular genetics testing that evaluates the methylation status of a genetic locus and is used to diagnose conditions in which these patterns may influence the presence or absence of disease.

Deletion / duplication analysis: Molecular genetics procedure used to identify large size deletion or duplication of DNA (typically between 40 base pairs and 40 Kilobases) within a gene.

Detection of chromosome alterations large in size: Cytogenetic testing to identify any change in the normal structure or number of chromosomes.

Detection of microdeletion / microduplication: Cytogenetic testing to detect a chromosomal deletion or duplication spanning several genes that is too small (< 5 Megabases) to be detected by conventional cytogenetic methods.

Chromosomal instability: Cytogenetic testing to detect a type of genomic alteration in which chromosomes are unstable, such that either whole chromosomes or parts of chromosomes are duplicated or deleted

Analyte / enzyme assay: Biochemical techniques to measure the enzyme activity or an analyte that can be absent, reduced or increased in quantity, as a result of an abnormality in a metabolic pathway.

Protein expression: Biochemical procedure used to analyse quantitatively or qualitatively a specific protein through different techniques.

3. Techniques:

Sanger sequencing: Classical technique of DNA sequencing considered the gold standard for mutation detection and highly sensitive for the detection of point mutations, splice site mutations, and small insertions and deletions. It allows to confirm the pathogenic sequence variants identified by next generation sequencing (NGS). It constitutes the method of choice to confirm the diagnosis of a disorder known to be associated with a single locus or gene.

Next generation sequencing (NGS) (except WES): also known as high-throughput DNA sequencing, is the catch-all term used to describe a number of different methods that rely on parallel analysis of multiple DNA fragments (e.g., panel of genes).

Whole Exome Sequencing (WES): Application of the next-generation technology to determine the variations of all coding regions, or exons, of known genes.

PCR (polymerase chain reaction) based techniques: Techniques that rely on PCR to amplify stretches of DNA by creating many identical or near-identical copies, such as QF-PCR (Quantitative Fluorescence-Polymerase Chain Reaction) or QMPSF (Quantitative Multiplex Polymerase Chain Reaction of Short Fluorescent).

MLPA based techniques: High-throughput techniques used mainly for copy number quantification (deletions and duplications), but as well for specific mutations screening and methylation status analysis of genomic sequences (MS-MLPA).

Array based techniques: Techniques based on a microscopic ordered array of nucleic acids, proteins, small molecules, cells or other substances that enables parallel analysis of complex samples.

Microsatellite analysis: Analysis of simple sequence repeats, a type of genetic polymorphism commonly used for mapping, linkage analysis and to trace inheritance patterns.

BS-Pyrosequencing (Bisulfite pyrosequencing): Technique that allows for detailed and high resolution analysis of DNA methylation at specific genomic regions.

FISH (fluorescent *in situ* hybridization): Molecular cytogenetic technique used to detect and localize the presence or absence of specific DNA sequences on chromosomes.

Multicolor FISH (M-FISH) / spectral karyoptyping (SKY): SKY and M-FISH use "whole chromosome paint" DNA probes, which are labelled with a unique fluorescent colour for each of the 24 pairs of human chromosomes. The technique visualizes and identifies chromosomal material in marker chromosomes and subtle translocations whose origin cannot be determined by other cytogenetic techniques.

Karyotyping: Karyotyping is a test to identify and evaluate any major chromosomal anomaly analyzing the size, shape, and number of chromosomes in a sample of cells.

Chromosome breakage analysis: Cytogenetics technique for assessing genomic instability performed on metaphasic caryotypes. Chromosome breaks occur either as a result of damage to DNA (by e.g. radiation or chemicals) or as part of the mechanism of recombination like in Fanconi anemia disease and other genetic disorders with elevated rates of chromosomal breakage or instability, leading to chromosomal rearrangements.

Immunohistochemistry: Biochemical testing to detect the presence of specific proteins in cells or tissues by means of a specific antigen/antibody reaction tagged with a visible label.

Western blot: A molecular genetic technique to separate proteins, by running on a gel, and identification of the proteins by immunological staining techniques.

4. Purposes:

Risk assessment: Evaluation of the likelihood of developing a specific condition based on genetic risk. It includes cancer genetic markers of susceptibility.

Pre-symptomatic diagnosis: Tests for variants causing or associated with diseases or disorders known to be inherited in the family, often with adult-onset symptoms. (e.g.: Huntington's disease, hemochromatosis, early onset Alzheimer's disease)

Pre-implantation diagnosis: Genetic testing performed on a small number of cells from a human embryo prior to uterine implantation as part of assisted reproduction procedures.

Antenatal diagnosis: Diagnostic procedures testing for diseases or conditions in a foetus or embryo before birth. Invasive methods for antenatal diagnosis include genetic tests after amniocentesis and chorionic villus sampling. Common non-invasive techniques include examinations by ultrasonography and maternal serum screens (i.e. Alpha-fetoprotein) but also blood tests for aneuploidies based on detecting foetal DNA present in maternal blood.

Post-natal diagnosis: All diagnosis tests carried out after birth in order to identify or confirm a disease or condition following a clinical diagnosis but also a suspicion due to family history before symptoms are declared.

Pharmacogenetics: Targeted tests for variants associated with pharmaceutical dosage choice or adverse reactions.

Newborn screening: Targeted tests for recessive genetic disorders (e.g., phenylketonuria, cystic fibrosis, sickle-cell anemia) performed on every newborn. These tests are part of a public health program and the number of diseases screened is set by each country.

Somatic genetics: Targeted tests completing the diagnosis obtained by pathologic or hematologic techniques in order to determine the best therapeutic solution and the prognosis of the disease.