

Procedural document: Data collection and registration of diagnostic tests in Orphanet

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I. INTRODUCTION

1.1. Purpose/objectives

For patients affected by a rare disease, obtaining a timely and accurate diagnosis is key in accessing appropriate medical expertise. Orphanet offers, amongst a range of expert resources on rare diseases, a directory of diagnostic tests to help with this process.

This document aims to define the set of criteria used to select, register and update diagnostic tests in Orphanet. Tests covering non-rare diseases in the case of the specialty of molecular genetics are also registered, as Orphanet is the reference database for genetic testing in Europe.

1.2. Disclaimer

- This procedural document is part of the OrphaNetWork Direct Grant (831390) which has received funding from the European Union's Health Programme (2014-2020).
- The content of this procedural document represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

1.3. Range of application

The present procedural document applies to all the diagnostic tests registered in Orphanet. The registration and update of the diagnostic tests is performed by the Orphanet national teams (ONT) having signed a Network Agreement and a Data Transfer Agreement (DTA) with the Orphanet Coordinating Team (OCT).

1.4. References

- [Orphanet Standard Operating Procedures](#)
- [Glossary and representation of terms related to diagnostic tests](#)
- EQA providers (EMQN, CF-Network, GenQA)
- [Regulation \(EC\) N°141/2000 of the European Parliament and of the council of 16 December 1999 on orphan medicinal products](#)
- [Commission Expert Group on Rare Diseases – Recommendation on cross-border genetic testing of rare diseases in the European Union \(19 November 2015\)](#)

1.5. Definitions

Accreditation: Formal recognition of technical competence in performing specific types of testing by complying with specific management and technical requirements.

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.

Constitutional genetic test: diagnostic test that consists in detecting a genetic alteration that is present in the organism since its conception and that are transmissible to offspring.

Array CGH (*Array comparative genomic hybridization*): Technique used to detect copy number variations (losses or gains of chromosomal material), uniparental disomy (UPD), regions with an absence/loss of heterozygosity (AOH/LOH) Depending on the method used, this technique may detect copy number variations, UPD, AOH/LOH across the whole genome, or in a specific chromosome, chromosome segment, or gene. It is primarily used for the diagnosis of dysmorphism, congenital abnormalities, learning difficulties, developmental delay and for detecting genomic abnormalities in cancer

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

Data transfer agreement (DTA): Contract between the providing and recipient institutions that governs the legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the transfer of such data between the parties.

Diagnostic test: A biological analysis performed in a clinical setting by the laboratory declaring the activity to:

- Diagnose or confirm the diagnosis of a disease,
- Test the response to therapies,
- Assess the likelihood of developing a specific condition based on a genetic risk.

EQA provider: Private or public network organizing EQA scheme(s).

External quality assessment (EQA): A system of objectively assessing the laboratory performance by an external agency (known as EQA providers) through the comparison of the lab performance against an agreed independent standard.

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

Information scientist (IS): Member of an Orphanet National Team, responsible for the data collection and registration of data.

Medical laboratory: Laboratory performing diagnostic tests in a clinical setting. If the laboratory has an official designation from a government institution to perform one of its tests, the information is reported on the test as being officially designated.

Microdeletion/microduplication syndromes: Disorders caused by microscopic and submicroscopic (typically 1 to 3 megabases) deletions or duplications of contiguous genes in certain parts of chromosomes.

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).

National websites: Tools to communicate at national level on the activities of the ONT, on events, and on national rare disease policy. The national website is a national entry point to the Orphanet portal in the 8 available languages (Dutch, English, French, German, Italian, Spanish, Polish and Portuguese).

Objective: Category in Orphanet that indicates the goal of a diagnostic test (e.g.: Targeted mutation analysis)

Orphanet online registration tool: service allowing the professionals to register and/or update their activities related to rare diseases in the Orphanet database

Orphadata: [Website](#) providing the scientific community with comprehensive, high-quality datasets related to RD and orphan drugs, in a reusable format.

Orphanet coordinating team (OCT): French US14 Inserm based team who coordinates the Orphanet Network, produces the English Orphanet Nomenclature and its scientific annotations and is also responsible for coordination of the production of the scientific content and of all Network activities including translation.

Orphanet national teams (ONT): Teams located in each participating country of the Orphanet network, and endorsed by national authorities. An ONT is composed, at least, of a country coordinator who is responsible for the national Orphanet activities including translation. It can also include one or several information scientists, translation staff and a project manager.

Panel of genes: Collection of targeted genes thought to be relevant for particular diseases or conditions that are analysed together in a single diagnostic test. Genes present in a panel are usually linked by common biological pathways, or known disease associations.

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

Purpose: Context in which the test is performed (e.g.: postnatal diagnostic). For more information on the terms used for purposes, please refer to the annex of this document or to the [Glossary and representation of terms related to diagnostic tests](#).

Ring chromosomes: structurally abnormal chromosome in which the end of each chromosome arm has been lost and the broken arms have been reunited to form a ring.

Specialty: First level of the technical procedure used in Orphanet to represent a diagnostic test. It represents the main method category of a diagnostic test (e.g.: Molecular genetics). For more information on the terms used for specialties, please refer to the annex of this document or to the [Glossary and representation of terms related to diagnostic tests](#).

Technical procedure: Test methodology defined in Orphanet with a three-level representation: specialty, objective and technique. For some specialties, objective and technique are not further developed (e.g. parasitology). For more information on the technical procedure representation and the terms used, please refer to the annex of this document or to the [Glossary and representation of terms related to diagnostic tests](#)

Technique: Third level of the technical procedure used in Orphanet to represent a diagnostic test. It indicates the specific technology used when performing a diagnostic test to reach the objective (e.g. Sanger sequencing). For more information on the terms used for techniques, please refer to the annex of this document or to the [Glossary and representation of terms related to diagnostic tests](#).

Rare disorder (RD): A rare disorder is defined according to the European legislation defining a prevalence threshold of not more than 5 affected persons per 10'000 (Regulation (EC) N° 141/2000 of the European Parliament and of the council of 16 December 1999 on orphan medicinal products).

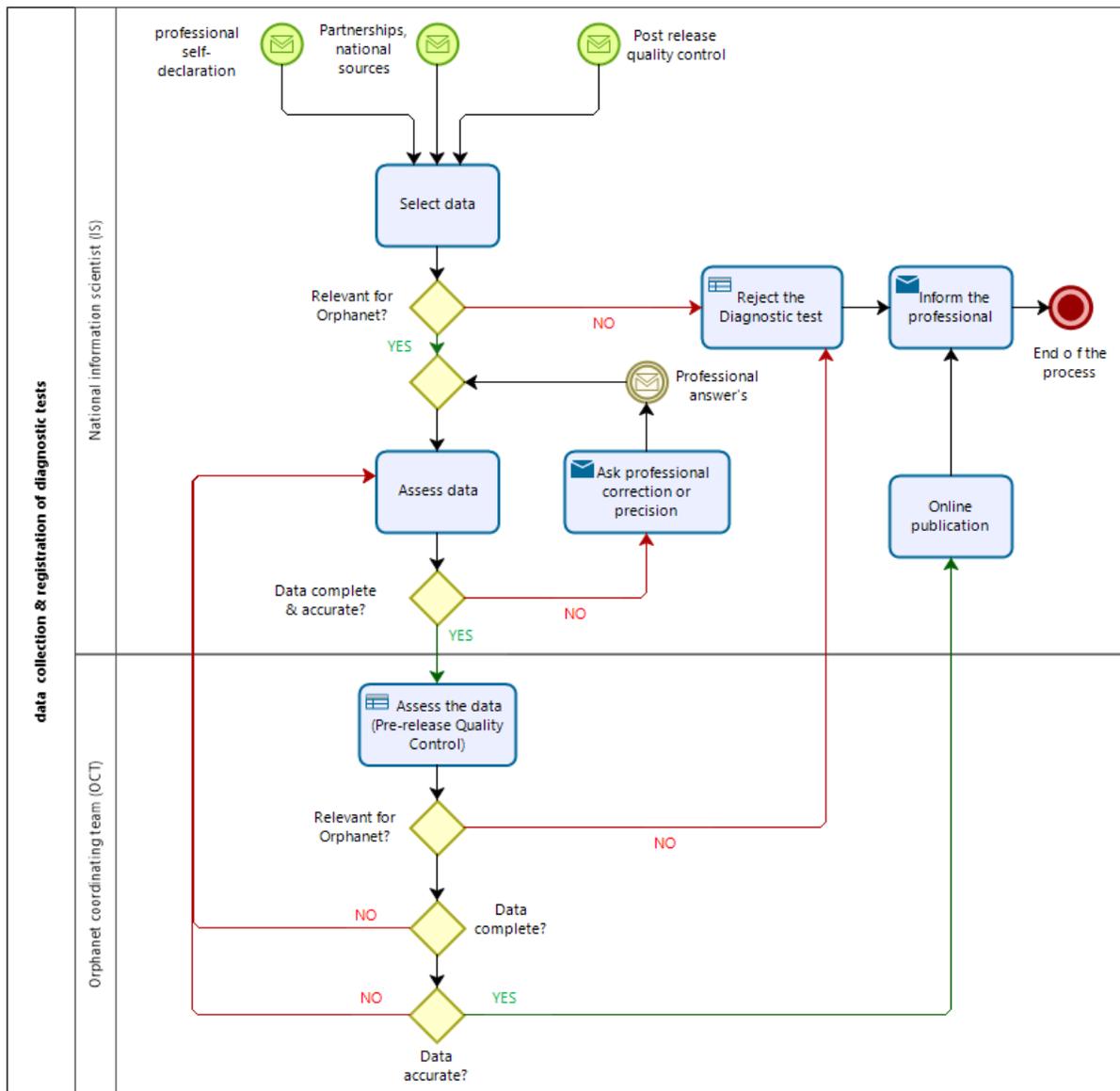
1.6. Filing and updates

This document is updated by the coordinating team as often as necessary and at least once a year. The most up-to-date version is available on the Orphanet website: https://www.orpha.net/consor/cgi-bin/Education_Procedure.php?lng=EN

II. METHODOLOGY

2.1. Flowchart

The general process for the data collection, registration, validation and quality control of the diagnostic tests is presented below:



2.2. Description

The process of registration/update of diagnostic tests starts with:

- Professionals declaring their activity through the [Orphanet online registration service](#) or in any communication channel with Orphanet teams (e-mail, phone call, etc.).
- Data obtained through a partnership (e.g. with the national health authorities)
- A post-release quality control project focused on diagnostic tests

An annual update is organised and launched by the OCT. All the professionals responsible of diagnostic tests registered in the database are invited to review and update their activities through the [Orphanet online registration service](#). National teams are responsible for the follow-up of their feedback.

a) Sources of information

National teams are in charge of identifying the sources of information for the testing activity of medical laboratories in their country, and are advised to establish partnerships with them to obtain this information.

In case of establishing a partnership, national teams must inform the OCT, as some types of partnerships require the signature of a data transfer agreement (DTA).

The sources of information can be official (i.e. governmental organizations) or non-official (e.g. national human genetic societies, other learned societies, EQA providers¹, etc.).

If there is no source to obtain this information, or the source(s) do not allow an exhaustive coverage of the testing activity in the country, national teams are in charge of identifying the laboratories in their country performing diagnostic tests and inviting them to declare and update their activity through the [Orphanet online registration service](#).

b) Data selection

ONT are involved in collecting and registering the information on diagnostic tests for their own country. They must perform a data selection to verify that each diagnostic test, regardless of the source, meets the inclusion criteria for Orphanet. This applies for new tests and for updates.

There are three general inclusion criteria:

- Tests should be performed in a clinical setting (tests carried out on a research basis should be registered as research projects and not as diagnostic tests).
- Tests should be performed by the medical laboratory itself.
- Only tests requiring specific technical competence should be included. These criteria have to be adapted to the national context by each team and included in the Orphanet national website.

¹ Orphanet has a collaboration agreement with three EQA providers : CF Network, CEQAS and EMQN

There are specific inclusion criteria² depending on the specialty of the test, for:

- Molecular genetics: All constitutional genetic testing analyses are collected, even for non-rare diseases and pharmacogenetics².
- Cytogenetics:
 - o Conventional cytogenetic analyses (karyotypes, G-banding, etc.) are only registered in Orphanet if they are relevant for the country according to the specific technical competence available in the country.
 - o Cytogenetic analyses like FISH, MLPA or array-CGH are registered in Orphanet only if they are designed for specific microdeletion/microduplication syndromes. Tests for chromosome number anomalies and ring chromosomes done by FISH (e.g. Trisomy 11) are not registered in Orphanet, as their detection does not require a specific expertise in molecular cytogenetics (unless if it is considered as a specific technical competence in the country).
- Biochemical genetics: Only tests requiring special metabolic investigation and allowing for establishing a diagnosis of a rare disorder should be considered: enzyme assays, key metabolite analyses, or functional assays when required.
- Bacteriology, virology, parasitology, mycology: If the country has centres/laboratories of reference for infectious diseases, only their tests should be listed for a given disease.
- Anatomical-pathology, immunology, hematology, imaging: The level of expertise required has to be adapted to the national context by each team and disclaimed in the Orphanet national website.

c) Data assessment

If the diagnostic test complies with the Orphanet inclusion criteria, the ONT analyses the information to check that the mandatory dataset (cf below) is provided and that it is coherent, and eventually introduce the necessary corrections before submitting to international pre-release quality control (see below).

In case of inconsistency or missing information, the ONT will contact the professional in order to clarify or obtain the information needed.

i. Orphanet dataset for diagnostic tests

a) Mandatory dataset

- Name of the diagnostic test in local language and in English,
- Name and details of the laboratory performing the test,

² The technical terms are defined in Annex 1

- Name and personal details of at least one professional responsible for the test³,
- The specific disorder(s) covered by the test,
- The gene(s) and/or panel of genes covered by the test, if applicable,
- The purpose(s) of the test,
- The technical procedure(s) used in this test,
- Indication whether the laboratory is officially designated for the diagnostic test,
- Indication whether the diagnostic test can be published by Orphanet.

b) Optional dataset

The optional dataset includes data regarding the laboratory quality management: EQAs and accreditations.

d) Pre-release quality control (PrRQC)

Once the candidate diagnostic test passed the national assessment, the coordinating team performs a pre-release quality control to assess the relevance and correctness of data collected by the national teams.

This quality control is mainly focused on the diseases and (panel of) genes linked to the test, as well as on the coherence of the scientific dataset (technical procedure(s), purpose(s) and the English label of the test).

In case some information is missing or needs correction, the form gets sent back to the national teams.

e) Data publication

Once all the quality control steps passed, the information on diagnostic tests is accessible on the [Orphanet website](#) and can be retrieved from [Orphadata](#) after signing a DTA. Once published, the ONT are in charge of informing the professional(s) that the diagnostic test has been published.

f) Post-release validation

The post-release quality control for diagnostic tests includes the quality control projects, which are organized by the coordinating team on a regular basis to check the completeness and consistency of the data (e.g. non molecular genetic tests linked to a non-rare disease; molecular genetic tests not linked to a gene or panel of genes).

³ Please note that all professionals registered in Orphanet have at any time a right of access, rectification, erasure, restriction of processing of their personal data as described in the GDPR by writing to gdpr.orphanet@inserm.fr

III. ANNEXES

3.1. Annex 1 – Technical procedure representation

Extracted from [Glossary and representation of terms related to diagnostic tests](#) :

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)

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

Biochemical genetics:

- Analyte / enzyme assay

- Protein expression
 - Immunohistochemistry
 - Western blot

Parasitology

Bacteriology

Virology

Mycology

Immunology

Hematology

Pathology

Imaging

Other

3.2. Annex 2 – Glossary of technical procedures & purposes

Extracted from [Glossary and representation of terms related to diagnostic tests](#) :

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.

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.

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 karyotyping (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 karyotypes. 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.

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.

For any questions or comments, please contact us: contact.orphanet@inserm.fr

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