

**EuropaBio
Principles for
Genetic Testing
and Testing for
Genetically-Driven
Risk Factor**

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List of abbreviations

AMD	AGE-RELATED MACULAR DEGENERATION
ASCVD	ATHEROSCLEROTIC CARDIOVASCULAR DISEASE
EHDS	EUROPEAN HEALTH DATA SPACE
EMA	EUROPEAN MEDICINES AGENCY
GDPR	EU GENERAL DATA PROTECTION REGULATION
HCP	HEALTHCARE PRACTITIONERS
HMA	HEADS OF MEDICINES AGENCIES
HTA	HEALTH TECHNOLOGY ASSESSMENT
IVDR	IN VITRO DIAGNOSTIC MEDICAL DEVICES REGULATION
LP(A)	LIPOPROTEIN(A), A GENETIC RISK FACTOR FOR ASCVD
MS	MEMBER STATES
NBS	NEW-BORN SCREENING
NGS	NEXT GENERATION SEQUENCING
RWE	REAL-WORLD EVIDENCE
SMA	SPINAL MUSCULAR ATROPHY

Executive Summary

Advances in science and technology have greatly improved our understanding of the genetic basis of disease, which have made it possible to redefine many diseases at higher resolution and target them with more precise treatments such as cell and gene therapies.

Increased access to genetic testing is a significant opportunity for patients and healthcare systems in Europe by supporting the deployment of targeted therapeutic strategies. With knowledge, people at risk of developing diseases may take steps towards prevention. New therapies can transform lives if they reach the right patients at the right time. Whether for screening, early or confirmatory diagnosis, or patient stratification, genetic testing can support medical decision-making, empowering patients and helping healthcare systems use the most appropriate treatments.

To support the uptake of genetic testing, EuropaBio propose a set of 12 policy principles and associated recommendations across the following areas:

- ◆ Regulatory pathways
- ◆ Funding and access
- ◆ Infrastructure and workforce
- ◆ Ethics and society

EuropaBio invite policy-makers and other relevant stakeholders to engage with us on this topic and unlock the path of innovation for next generation medicines to the benefit of European patients, healthcare systems, and society.



Introduction

Advances in science and technology have greatly improved our understanding of the **genetic basis of disease**, have made it possible to **redefine many diseases at higher resolution**, and target them with **more precise treatments**. These advances have already transformed the treatment of many cancers and rare diseases and are expected to challenge the standard of care in other underserved areas, with profound impacts on healthcare biotechnology.

A move towards **molecular classification of cancer** has given rise to precision oncology, which takes aim at specific pathways unique to a given type of cancer. **Rare diseases, most of which are genetic in origin**, have also seen major advances; for example, faulty genes can be replaced through gene therapy or downregulated by gene silencing.

The development of these treatments has been enabled by **substantial technological advances in genetic testing**, such as the development of next generation sequencing (NGS), which allows an entire human genome to be sequenced within a day. Reduced cost and increased availability of genetic testing are enabling **genome-driven medical decision-making** in the treatment of disease, but also in disease prevention (e.g., variant screening), family planning (e.g., carrier status, prenatal testing), and public health.

Increased access to genetic testing is a significant opportunity for patients and healthcare systems in Europe. New **therapies can transform lives if they reach the right patients at the right time**, which in some cases may be before symptoms emerge. With knowledge, people at risk of developing diseases may take steps towards prevention.

However, in Europe, the topic is sometimes viewed with suspicion by citizens and healthcare providers alike, especially when it comes to the screening of pre-symptomatic individuals.

The topic of genetic testing and screening is multifaceted and **raises many questions in areas of regulation, funding and access, infrastructure, and ethics**. To advance the discussion, EuropaBio is proposing a set of **12 policy principles** and recommendations for genetic testing and (non-genetic) testing for genetically-driven risk factors to **benefit European patients, healthcare systems, and to foster innovation**.

What is genetic testing?

Genetic tests and (non-genetic) tests for genetic risk factors are medical tests used to identify mutations in genes that correlate to a patient's risk of developing a certain condition. Tests can be performed from a sample of blood, skin, amniotic fluid (prenatal screening), or other tissue. Procedures can be as simple as a cheek swab from inside the mouth.

Genetic testing can be used to screen or test for a growing number of diseases or risk factors, including breast and ovarian cancer, celiac disease, age-related macular degeneration (AMD), Parkinson's disease, and rare diseases such as cystic fibrosis.

Genetic testing (and testing for genetic risk factors) can take on various forms, including single gene testing, genetic panel testing, whole exome or genome sequencing, tissue (e.g., tumour) or liquid biomarker testing. Even imaging techniques can be useful for determination of genetic risk factors. Tests fall into one of four main categories:

- **Screening:** Detection of pre-symptomatic patients in an apparently healthy, asymptomatic population
- **Early detection:** Detection of early signs and symptoms of disease
- **Confirmatory diagnosis:** Confirmation of screening or primary diagnosis
- **Patient stratification:** Identification of patients most likely to respond to a targeted therapy

Benefits of genetic testing for patients, healthcare systems, and society

Whether for screening, early or confirmatory diagnosis, or patient stratification, genetic testing can yield significant benefits for patients, healthcare systems, and society. With the appropriate counselling and infrastructure in place, genetic testing at any stage can **provide information to enable medical decision-making**.

Screening healthy, pre-symptomatic populations for disease risk factors can inform lifestyle choices or preventive treatment, reducing the need for more costly or invasive treatment at a later stage, and improving outcomes. While screening programs have costs, those costs can be more than offset by healthcare savings from early treatment.^{1,2} Disease prevention or delayed onset can also provide broader societal benefits by enabling more productive lives and better long-term planning for those affected, their caregivers, and their families. For degenerative diseases, symptom onset may already be associated with irreversible damage. This is why new-born screening (NBS) programs for degenerative diseases, such as spinal muscular atrophy, are so important.

Genetic variant or biomarker testing can provide **early diagnosis** before full clinical disease manifestation. This can enable earlier treatment, with more treatment options, fewer disease complications, better quality of life and better prospects for those affected, especially for progressive conditions. Early treatment is also less costly for healthcare systems. It takes on average 4.8 years and 7 specialists for a rare disease patient to get an accurate diagnosis³; the journey is not only burdensome, but also costly to the healthcare system. Early access to genetic testing can often provide an earlier diagnosis. Even when no approved treatments are available, patients with early diagnosis may benefit from knowing their prognosis or have the opportunity to participate in clinical trials.

Obtaining **confirmatory diagnosis** is the most well-established rationale for testing. Confirmatory diagnosis can provide clarity and inform the right treatment. When no treatment is available, confirmatory diagnosis through genetic testing may still be useful to the patient for life- and/or family-planning purposes.

¹ Kwan, A.; Abraham, R.S.; Currier, R.; Brower, A.; Andruszewski, K.; Abbott, J.; Baker, M.; Ballow, M.; Bartoszesky, L.E.; Bonilla, F.A.; et al. Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States. *JAMA* 2014, 312, 729–738.

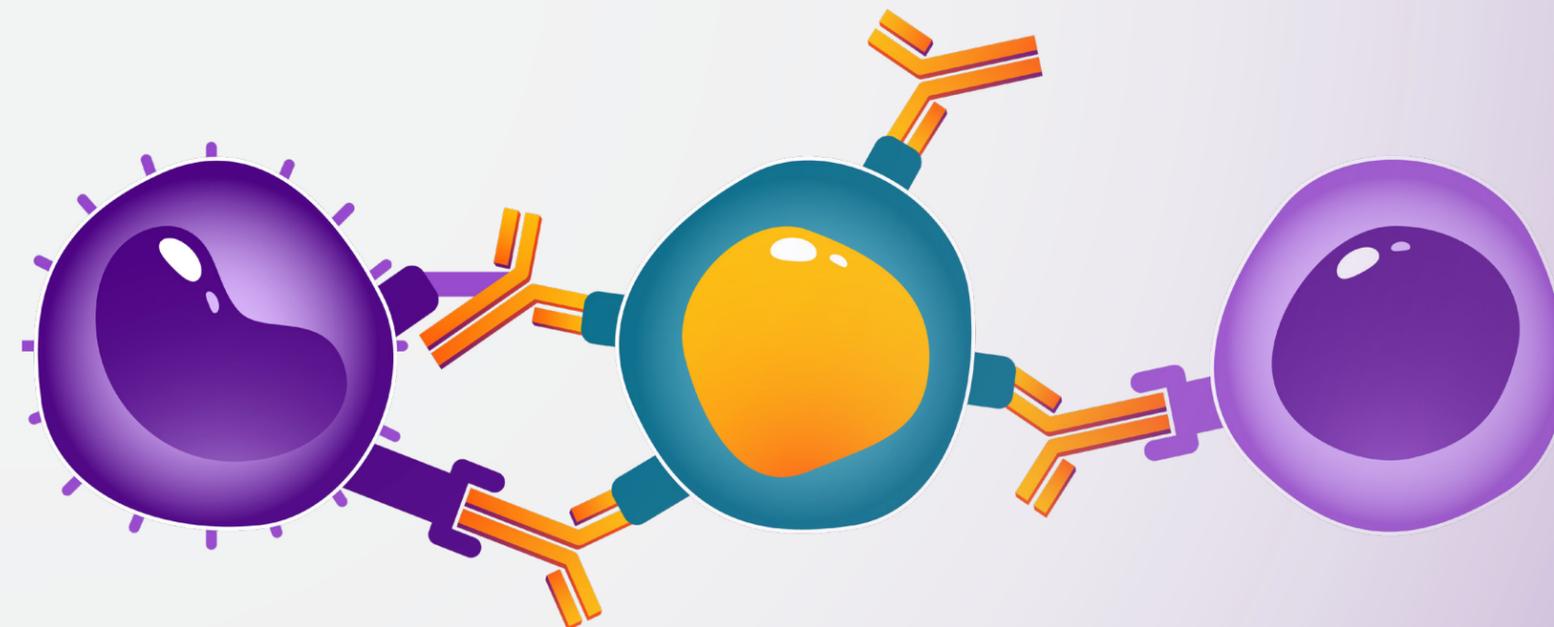
² Shih, S.T.F.; Keller, E.; Wiley, V.; Farrar, M.A.; Wong, M.; Chambers, G.M. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. *Int. J. Neonatal Screen.* 2022, 8, 45.

³ Wakap et al. 2019; *Global Genes: RARE Facts* 2020.

Patient stratification enables precise definition of the disease which can unlock targeted treatments that are more effective and have fewer side effects. Patient stratification is also performed in the context of pharmacogenomic evaluations to predict an individual's likely response to treatment. It can also be used to exclude unnecessary or ineffective treatment, benefiting patients and healthcare systems.

Genetic Testing Principles and Policy Asks

EuropaBio believes that genetic testing is helpful and desirable when it provides actionable information that can inform medical decision making. It can empower patients and help healthcare systems use the most appropriate treatments. Building on the experience of its members, EuropaBio proposes a set of 12 principles and related recommendations for genetic testing spanning four main areas. These principles apply to various diseases and care settings, from primary genetic diseases and cancer to more common diseases such as cardiovascular and neurodegenerative disorders.





Regulatory pathways

Principle 1: *Regulatory frameworks should not be contradictory. They should be adapted to appropriately assess available evidence for novel technologies.*

In Europe, genetic testing is regulated by the In Vitro Diagnostic Medical Devices Regulation (Regulation (EU) 2017/746), which provides a high regulatory standard for genetic tests and devices. Other regulations, at EU and national levels, apply to the processing of genetic data and aspects of use in a clinical setting, and result in a fragmented EU testing landscape with at times conflicting rules and definitions. Thus, a lab in one EU Member State (MS) cannot easily provide tests to patients in other countries. Inconsistent implementation of the EU General Data Protection Regulation (Regulation (EU) 2016/679) across EU MSs results in different standards for obtaining consent for the use of data, which makes data sharing difficult and precludes building EU-wide databases. As technology advances, problems will compound.

Policy Recommendations:

- Regulatory bodies should be in constant dialogue with scientific experts and diagnostics companies to ensure regulations proactively anticipate developments in testing technology.
- Strengthen harmonisation across MS on the sharing of health data, including through the proposed European Health Data Space, guidelines and policy actions, or an EU level Code of Conduct.

Principle 2: *Value assessment evidence requirements for innovative tests should be aligned and harmonised across the EU. This requires dialogue between regulators, HTA bodies, payers, physicians, innovators and patients.*

While regulatory requirements for diagnostic tests in Europe are harmonised under the IVDR, value assessment criteria and evidence requirements differ between countries, leading to challenges in evidence generation. There is no direct link between regulatory approval and reimbursement, and key stakeholders such as patients are often excluded from the evaluation processes.

Policy Recommendations:

- Regulators and value assessment bodies should ensure their criteria are aligned and assessment procedures are synchronised, to minimise barriers to introduction of new tests (e.g., companion diagnostics for targeted therapies in cancer, inclusion of disorders in new-born screening programs).
- Stakeholders across countries should align on value assessment criteria for diagnostic tests and new technologies.
- Authorities should include patients and physicians in the decision-making process.

Principle 3: *Decision makers at all levels should coordinate to prevent access delays to screening and testing.*

Criteria and evidentiary review methodologies for inclusion of tests or disorders in screening programs should be standardised and programs updated frequently with opportunities for patient consultation.

Evaluation methodologies and criteria for inclusion of tests or disorders in screening programs (e.g., NBS panels) vary significantly between EU MS (and sometimes regions in the same MS) resulting in significant discrepancies in disorders screened. For examples, while some regions in Italy include over 50 diseases in their NBS panels, Luxembourg includes 5, and Cyprus includes 2 diseases.

Policy Recommendations:

- Countries and regions should share best practices in evidentiary review methodologies to overcome the heterogeneity in screening programs.
- Countries should implement clear decision-making pathways for inclusion of tests or disorders in screening programs (e.g., NBS panels) that are followed by all stakeholders involved.
- Increased coordination at EU level and between regional authorities to improve the sharing of best practices (e.g., learnings from NBS pilot in one region).



Funding and access

Principle 4: *Decision makers should consider the benefits of testing and screening to patients, society and the medical community, including long-term cost savings and the value of knowing for patients, when assessing technologies, diseases or biomarkers to inform funding and coverage decisions.*

Rationale: There are long-term economic benefits of screening and early detection. Early or preventive treatment can slow or stop disease progression and avert more costly or invasive treatment, disability or premature death. Early cancer diagnosis leads to significant overall healthcare savings including avoiding more radical and expensive treatment associated with later stage diagnosis. Patient stratification prevents use of ineffective treatments and provides better quality of life. Decision making and value assessment processes often focus on the budget impact of testing and treating more patients and do not always account for these longer-term benefits.

Policy Recommendations:

- Clear economic evaluation criteria should be part of the evaluation of a new testing and screening program.
- Value assessment frameworks for (companion) diagnostic tests should take a broad and long-term view of the economic impact of testing and screening (e.g., patients and their caregivers spending less time away from work if a disease is diagnosed and treated earlier).
- Health authorities should collect real-world evidence (RWE) of the economic impact of testing and screening programs after they are rolled out to support future decision making.

Principle 5: *Decision makers should define clear value considerations for diagnostic technologies, including for tests which are not associated with a particular intervention and RWE accepted where appropriate.*

Rationale: Many HTA and value assessment frameworks struggle to assess value appropriately when a test or technology is not associated with a particular treatment or intervention. This can include NGS, tests that monitor patients' health or detect adverse events. These challenges can prevent reimbursement and act as barriers to the uptake of genetic and genomic testing in care pathways.

Policy Recommendations:

- Reimbursement frameworks should be adapted to ensure they can appropriately evaluate new technologies, including those not associated with a particular intervention.
- Frameworks should be kept up-to-date as the technology advances.

Principle 6: *Responsibility for funding of diagnostics and screening lies with public health bodies, but industry may have a role to play in certain situations. Specific budget should be allocated for testing, anticipated via horizon scanning and integrated with other healthcare budgets.*

Rationale: Public health bodies are responsible for investing in disease prevention and early detection through testing and screening to support their citizens' health. Industry may help enable access to testing where health systems do not fund it, including through funding pilot programs to demonstrate the value of testing (e.g., NBS). In many countries there is lack of funding for screening and early detection, and budgets are often siloed, which means that the long-term cost savings that come from using diagnostics or other tests are realised in other healthcare budgets (e.g., medicines), which removes the cost saving incentive to increase use of tests or fund new tests.

Policy Recommendations:

- Public health bodies should take responsibility for funding diagnostics and screening where it has been demonstrated that they are cost-effective and beneficial to the health of the population. Hybrid funding of testing infrastructure may work for tests not associated with a specific disease or treatment.
- Countries should establish horizon scanning processes to anticipate future tests and funding requirements.
- Health system financial management should be extended to include all resources used during the patient journey instead of fee-for-service transactions impacting different budgets. This would allow savings from the entire care pathway (e.g., medicines, hospital care) to offset testing and screening costs.
- Funding for diagnostic testing should be an integral part of a sustainable healthcare system.



Infrastructure and workforce

Principle 7: *Investments in infrastructure, including in data analytics services, electronic health records, diagnostic equipment and laboratory capacity are needed to scale up testing and screening programs in the clinical setting.*

Rationale: Technologies like NGS need dedicated infrastructure, including molecular genetics laboratory equipment, analytical services and data capture (electronic health records). Investments in infrastructure are needed to make testing more widely available to support the broader needs of the population. It is vital that testing and screening infrastructure is resilient, e.g., to cyber threats. While data sharing and protection regulations for genetic data in EU countries are subject to the GDPR, interpretation varies across Member States.

Policy Recommendations:

- Governments should build sustainable diagnostic laboratory capacity to enable equal access. Capacity should accommodate the availability of precision medicines and anticipate future growth in use of testing technologies.
- Electronic health records should be rolled out to support optimal use of results from sequencing tests, on their own and in the context of a future EHDS.
- Data management systems should be interconnected and follow the highest standards for privacy and security to build trust in society and prevent undue disclosure and misuse of this information. A more uniform interpretation of the GDPR could harmonise data sharing and protection regulations to facilitate collaboration in genetic and genomic research.

Principle 8: *Healthcare professionals, including non-specialists, must be trained on screening and testing to increase uptake/ prescription and correct application and interpretation of tests.*

Rationale: Lack of training of physicians is a barrier to wider integration of genetic and genomic testing into clinical practice. As genetic testing becomes increasingly important to patient care, all HCPs should be educated in genetics and genomics to be able to correctly prescribe tests and interpret results. The increasing number of different guidelines on testing and screening from various stakeholders can present challenges for clinical decision makers. For example, non-lipid specialists are often unaware of Lipoprotein(a) as a genetic risk factor in Atherosclerotic cardiovascular disease (ASCVD) and testing of it.

Policy Recommendations:

- Educational programs for specialist physicians in therapy areas where genetics and genomics are currently available (e.g., oncology, rare diseases) to ensure lack of education is not a barrier to prescribing these tests.
- Training on interpretation of genomics testing should be included in continuing education programs for all non-specialist HCPs (e.g., GPs, secondary care nurses and physicians).
- Health bodies and industry should partner where appropriate to facilitate HCP education on screening and testing. There may be a role for EU bodies, e.g., European Medicines Agency (EMA), Heads of Medicines Agencies (HMA), or European Reference Networks to provide EU-wide guidance and best-practice sharing related to genetic testing.

Principle 9: *Diagnostic screening or testing should be available when a treatment is available. To allow patients to benefit from a treatment as soon as possible, the environment should be prepared in advance of the treatment's availability. Coordination between regulators, HTA, payers, policymakers, manufacturers, physicians, and patients is needed to make tests available with diagnosis and treatment guidelines available.*

Rationale: Payers' criteria for screening or testing programs frequently require that a treatment is available to address a diagnosis. However, testing programs (e.g., NBS) are often not synchronised with treatment availability, which can delay patient access to treatment, e.g., targeted therapies in cancer that require specific diagnostic tests.

Policy Recommendations:

- Professional societies should update clinical guidelines regularly, utilising horizon scanning, to ensure appropriate testing/screening recommendations are synchronised with treatment availability.
- Development of guidelines should include dialogue between all stakeholders including patients and industry.
- To ensure uptake of recommended tests, publication of guidelines should coincide with physician education, availability and reimbursement.



Ethical and societal

Principle 10: *A positive test result should lead to clear action, such as treatment, management or lifestyle changes.*

Rationale: A test should only be done when the result can benefit the patient. It is therefore important that the test result can lead to a clear action. However, decision makers (HCPs or payers) often take a narrow view of what this action could be, for example limiting it to prescription of a medicine. A broader view of an actionable result should include ability to make lifestyle changes, inform frequency of health checks, or enable longer term planning for patient and caregivers.

Policy Recommendations:

- The ability to take clear action after a test result should be a key criterion in evaluating it for adoption.
- Decision makers should take a broad view of what this action could be and include the ability to make lifestyle changes or improve adherence to medication.
- When a new test is implemented in care, there should be a clear pathway defined for a positive test result.

Principle 11: *Populations (age- or risk-based) should be screened where the best clinical outcome arises from intervening before the patient shows symptoms.*

Rationale: In some cases, screening or testing for a disease is most beneficial before the patient shows symptoms (e.g., NBS for spinal muscular atrophy (SMA), cervical cancer screening). Early detection enables early intervention and improves outcomes, especially in progressive disorders. In these cases, it is important that screening or testing programs are set up to ensure that the relevant populations are invited and screened before symptoms manifest.

Policy Recommendations:

- Part of setting up a testing and screening program for pre-symptomatic patients should be identifying the target population who could benefit (e.g., new-borns for SMA screening, at-risk groups for lung cancer).
- There should be clear, standardised criteria set out and evidence generated to identify these groups.
- Screening programs should ensure all members of the target population are invited on an opt-out basis.

Principle 12: *Testing for genes or biomarkers that indicate risk of developing disease should be based on informed consent and be available to individuals for whom there is evidence that identifying risks can improve outcomes.*

Rationale: Testing for increased risk of developing a disease (e.g., BRCA testing for breast cancer risk, Lp(a) testing in hypercholesterolemia,) can inform increased monitoring for disease development and the patient's lifestyle choices and future planning. It can also provide information to inform policy makers, e.g., health policy prioritisation or guideline development. Although the risk factor information is useful to patients and health systems, it should be the patient's decision whether to test. Information provided to patients during the consent process should make them aware of the potential use of their personal data.

Policy Recommendations:

- Clear criteria for when and to whom a test for elevated risk should be offered, and for the follow-up pathway.
- Patients should be informed of the benefits of the test as well as the implications of a positive result. Administering the test should then be based on patient co-created informed consent. Where necessary and possible, this information should include genetic counselling.
- Prior to screening the patient should be informed about use of their personal data, and impact for the patient and their family (e.g., BRCA testing for cancer risk).

About EuropaBio

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 79 corporate and associate members and bio-regions, and 19 national biotechnology associations in turn representing over 2300 biotech SMEs.

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