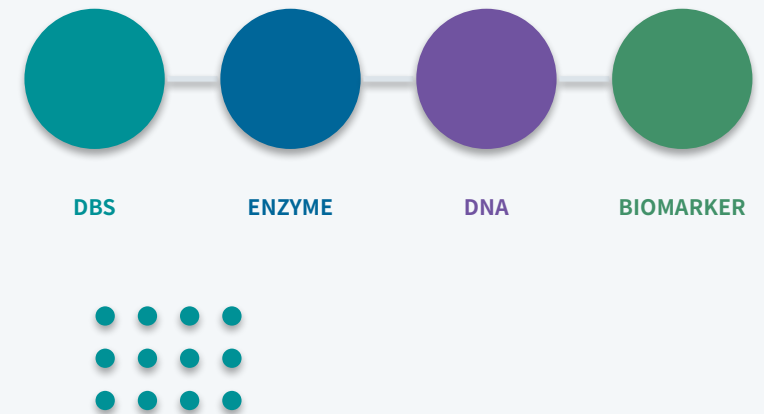


# Sponsored Diagnostic Services

POMPE • GAUCHER • ASMD

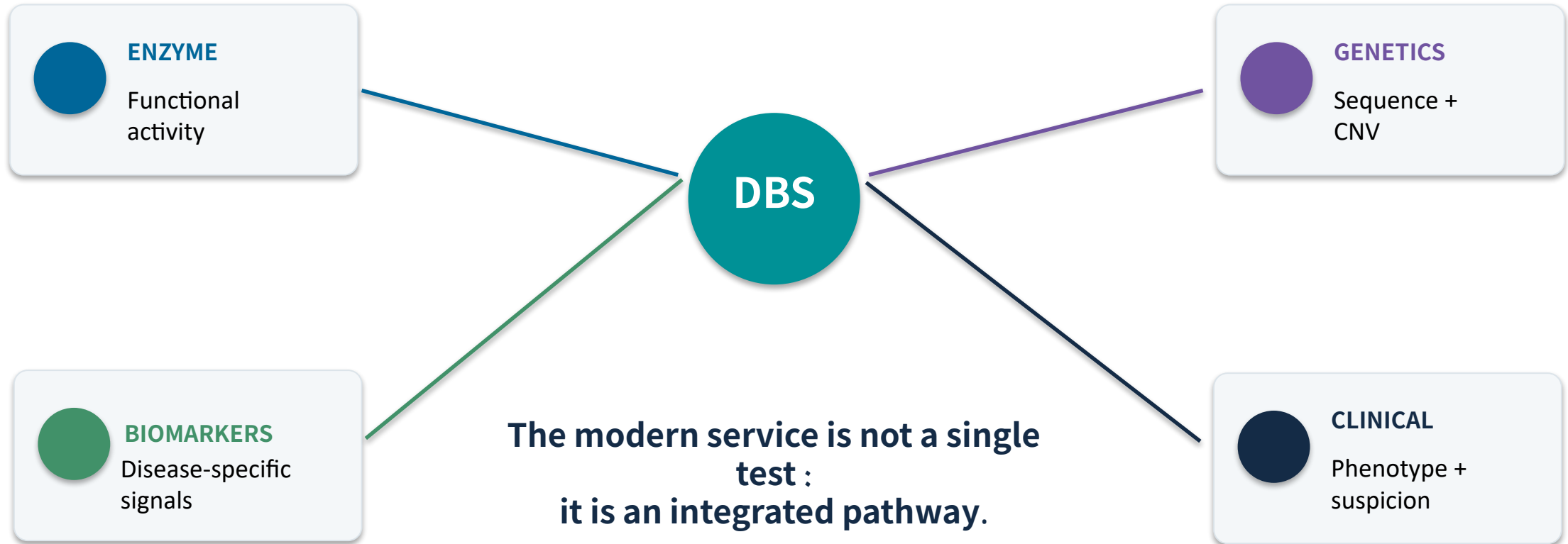
- ✓ From a dried blood spot to an integrated diagnostic pathway

Dr. Zahra Hadipour, MD - Clinical Genetic  
Medical Manager – SPC SANOFI/Rouquine Darou



# The diagnostic story in one picture

One small specimen can open several diagnostic dimensions



- ✓ How can we shorten the diagnostic journey for children with treatable lysosomal storage disorders?
- ✓ Briefly review the history of DBS-based diagnosis, how the technology evolved, and how today's integrated pathway combines enzyme activity, genetic testing and biomarkers.
- ✓ The key message is that DBS is not simply a blood-collection technique. It became a diagnostic-access strategy.
- ✓ Sanofi has several sponsored testing models in more than 100 countries.

# What does “Sanofi-sponsored” mean?

Separate scientific invention from sponsored diagnostic infrastructure

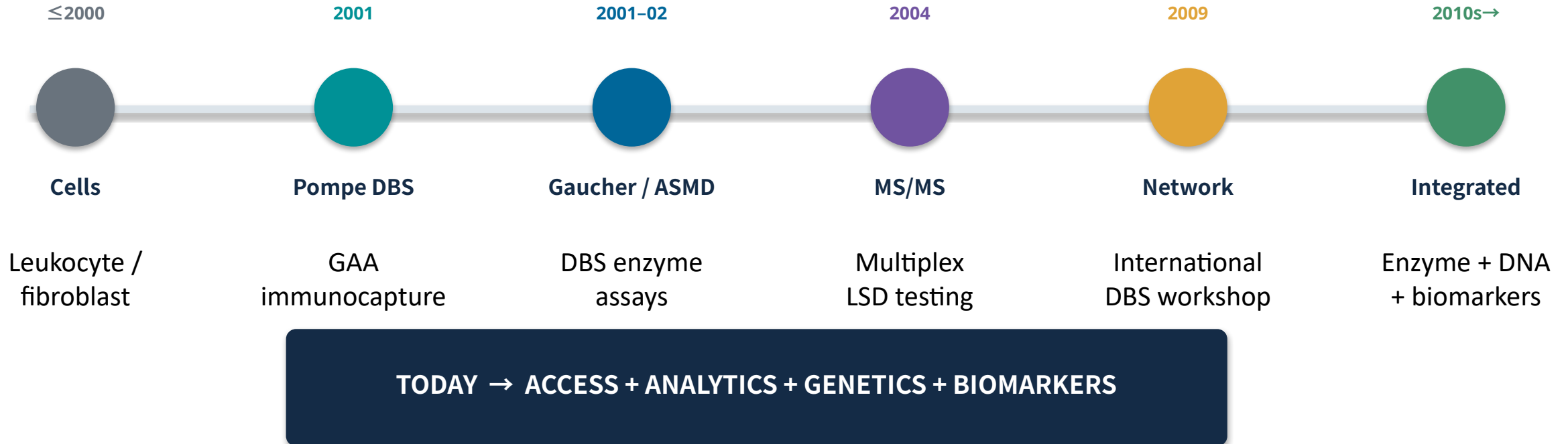


**Key message: Sanofi/Genzyme supported diagnostic infrastructure : it did not invent DBS.**

- ✓ DBS enzyme testing originated in academic and reference laboratories. Genzyme later helped move the technology into a broader diagnostic infrastructure.
- ✓ Genzyme sponsored an international DBS workshop in Amsterdam with approximately 40 experts from Europe, the United States, South America and Asia, and the meeting supported creation of a worldwide specialized DBS laboratory network.

# Global evolution: from specialist testing to integrated diagnosis

SANOFI | RARE DISEASE DIAGNOSTICS

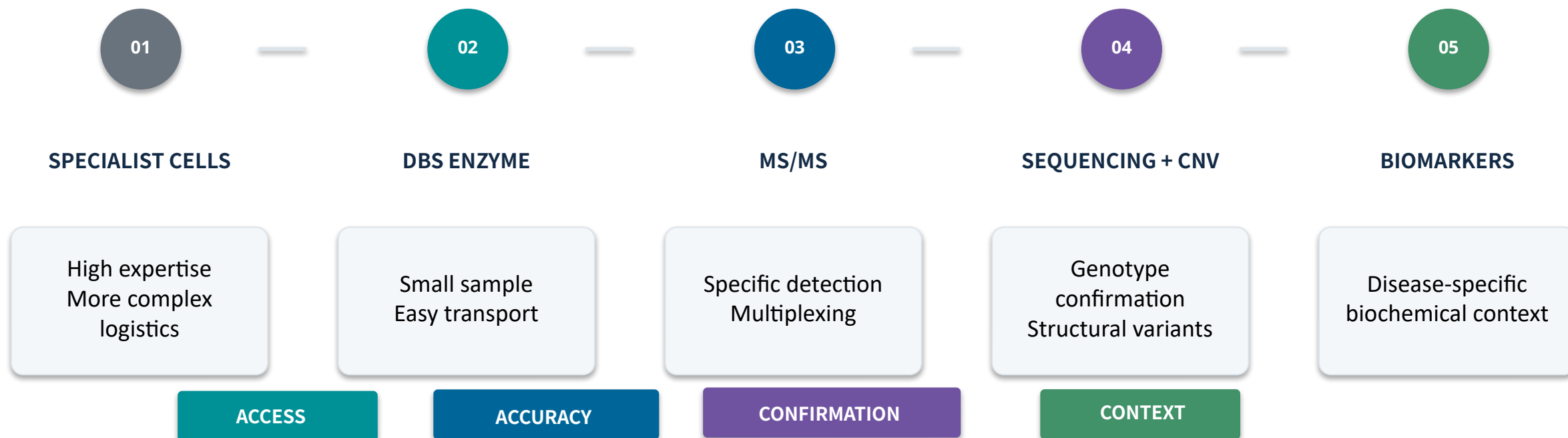


- ✓ The evolution can be understood in stages. Before DBS, diagnosis depended on leukocytes, fibroblasts or tissue.
- ✓ In 2001, a DBS GAA assay for Pompe was demonstrated in Australia.
- ✓ In Argentina demonstrated DBS assays for Gaucher and Niemann-Pick disease.
- ✓ Genzyme was supporting international discussion, quality systems and laboratory networking. The modern stage adds sequencing, copy-number analysis and biomarkers.

# How the methods evolved

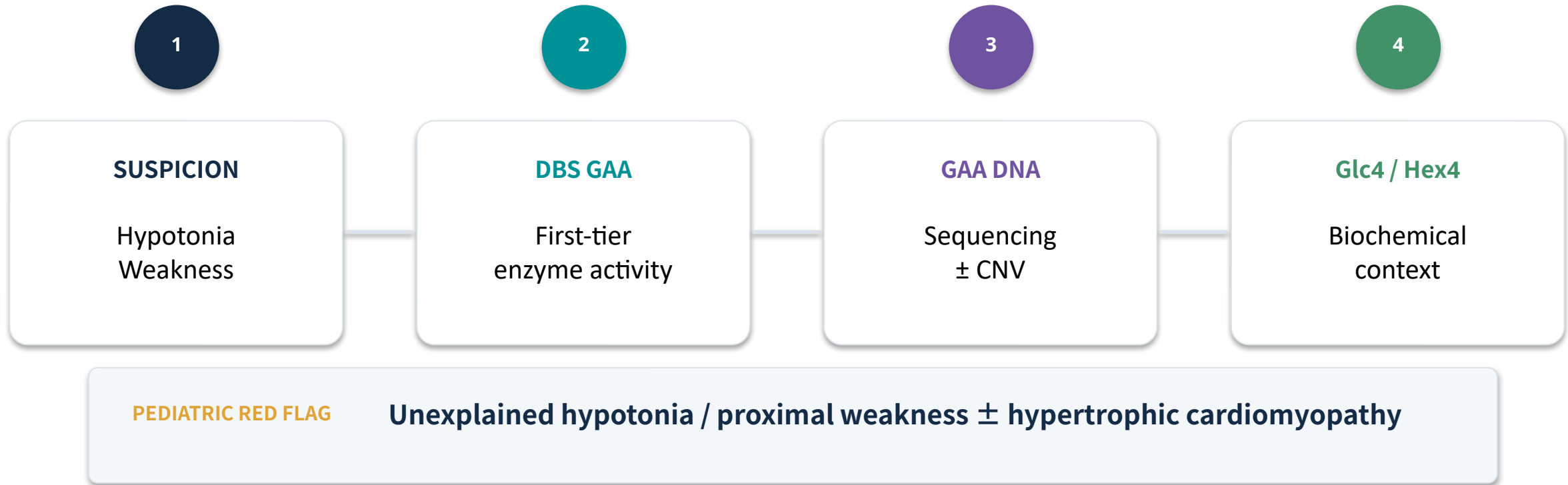
The strength is the combination ; not any single method.

Each innovation addressed a different diagnostic challenge



- ✓ The first generation was fluorometric or immunocapture testing. It was accessible and relatively simple but usually focused on one enzyme.
- ✓ The major analytical advance was MS/MS, which allowed multiple enzyme products to be measured with internal standards.
- ✓ The next advance was reflex genetics. Finally, biomarkers were incorporated to improve diagnostic confidence and provide information beyond the enzyme result.
- ✓ The modern pathway is not enzyme versus genetics. It is biochemical screening followed by molecular confirmation and, when useful, disease-specific biomarkers.

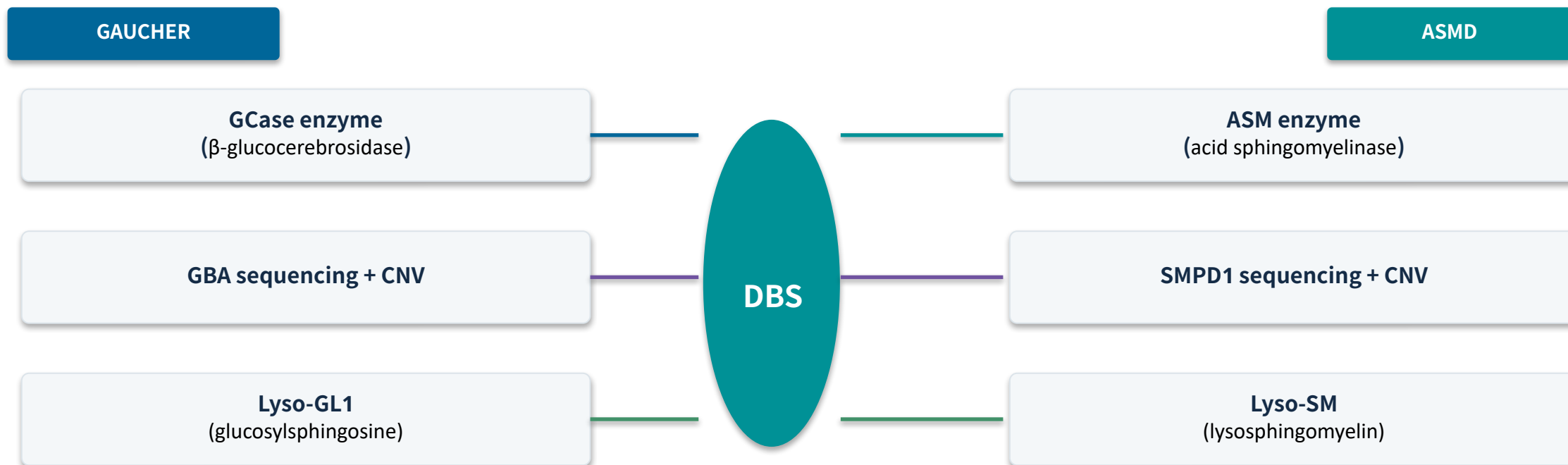
# Pompe: from clinical suspicion to confirmation



- ✓ For Pompe, the central biochemical target is acid alpha-glucosidase, or GAA.
- ✓ DBS GAA activity is an excellent first-tier test because it is rapid and minimally invasive.
- ✓ If deficient or borderline, the next step is GAA sequencing. Current sponsored workflows can also include copy-number analysis when needed.
- ✓ In infants, especially suspected infantile-onset Pompe, speed matters because treatment decisions are time-sensitive.

# Gaucher & ASMD: one DBS, two important pathways

SANOFI | RARE DISEASE DIAGNOSTICS



**Phenotypic overlap → parallel enzyme testing can broaden the diagnostic differential.**

- ✓ Gaucher and ASMD deserve special attention because they overlap clinically.
- ✓ Gaucher is associated with deficient beta-glucosidase activity and GBA1 variants; ASMD is associated with deficient acid sphingomyelinase and SMPD1 variants.
- ✓ Because the clinical phenotypes overlap, parallel GCase and ASM testing is more rational than a sequential single-disease approach when suspicion is broad.

# Why DBS is so powerful in pediatrics

Its strongest advantage is access and logistics



**SMALL**

Few drops



**SIMPLE**

Easy collection



**STABLE**

Dry transport



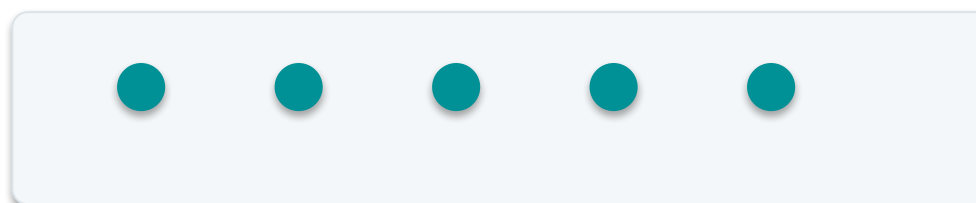
**CENTRAL**

Expert testing



**SCALABLE**

High throughput



**ONE SMALL CARD → SPECIALIST LABORATORY**

- ✓ The main superiority of DBS is not that it is always analytically superior to a leukocyte or fibroblast assay. Its real superiority is access.
- ✓ It requires little blood, is easy to collect in children, can be dried and transported, and allows a reference laboratory to test samples from distant regions.
- ✓ It is therefore particularly powerful for rare diseases where expertise is concentrated in a few laboratories. With MS/MS, the same DBS can support multiplex enzyme testing, and sequential Genetic Analysis.

# DBS enzyme assays: what improved with MS/MS?

## FLUORESCENCE / IMMUNOCAPTURE

- Accessible first-tier testing
- Targeted enzyme activity
- Practical laboratory workflow

## TANDEM MS/MS

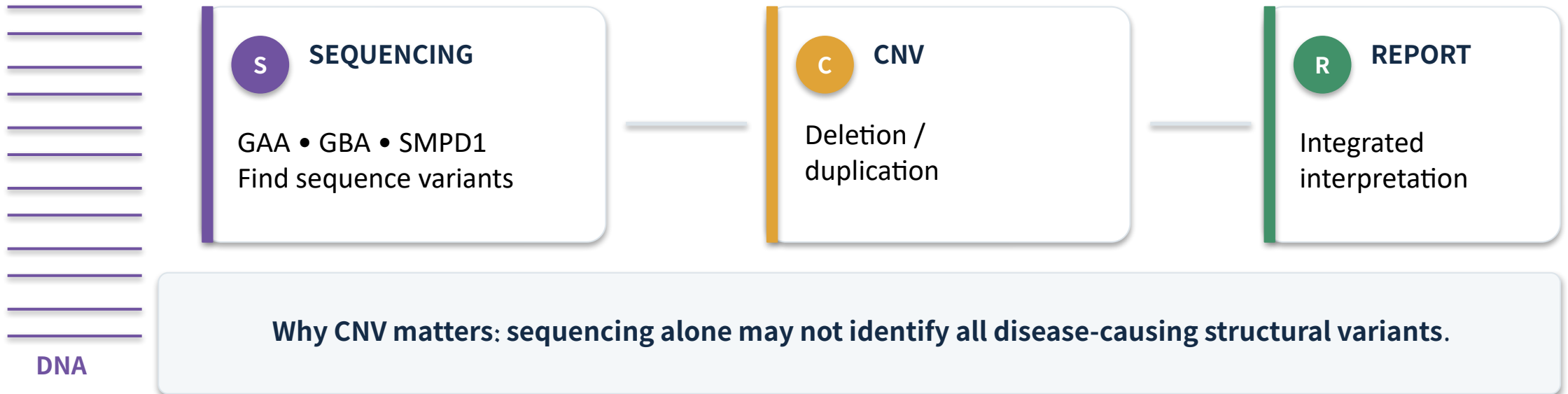
- Specific product detection
- Internal standards
- Multiplex + throughput

**MS/MS adds analytical specificity — but genetics and clinical context remain essential.**

- ✓ Fluorometric and immunocapture methods remain useful because they are relatively accessible and can be highly effective when validated.
- ✓ MS/MS adds analytical specificity, internal standards and multiplex capability.
- ✓ For Gaucher, a comparative study involving 528 samples showed that MS/MS beta-glucocerebrosidase testing eliminated false positives seen with fluorescence.
- ✓ MS/MS superior, we should specify: superior for analytical discrimination, multiplexing and throughput—not a replacement for molecular confirmation.

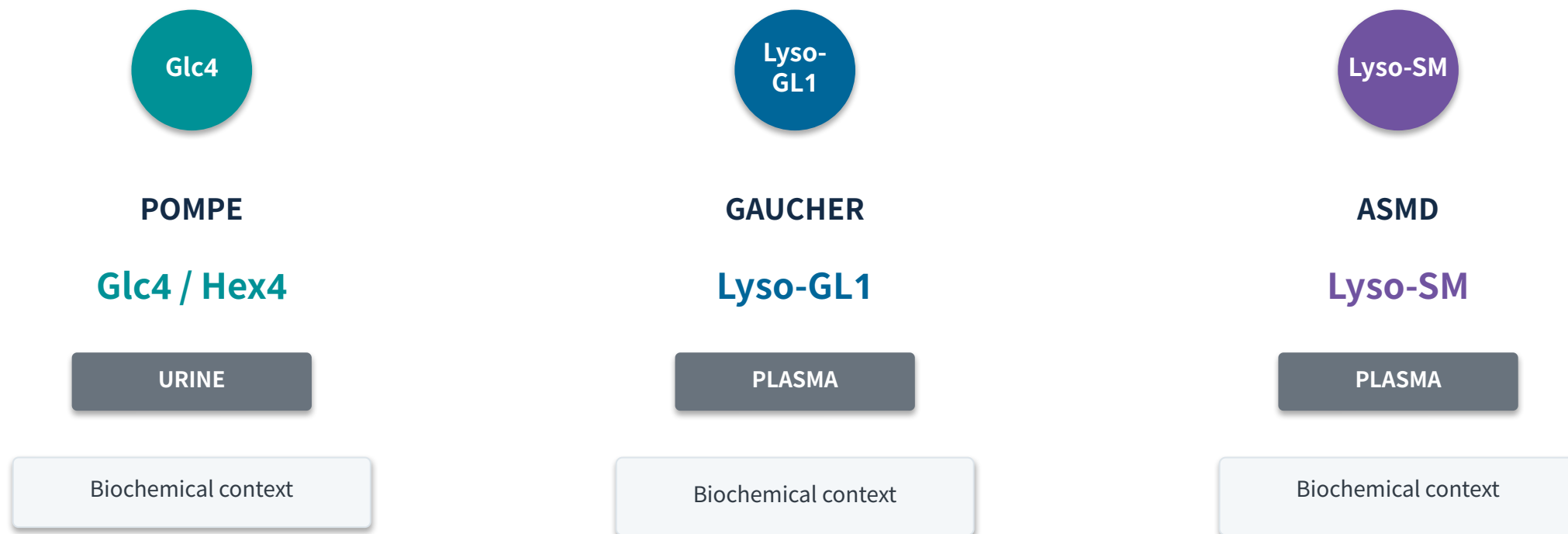
# Genetic analysis: sequencing + deletion/duplication (CNV)

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- ✓ Genetic testing is the second pillar.
- ✓ In Pompe, GAA sequencing identifies the causal variants and can be particularly important in infantile-onset disease.
- ✓ In Gaucher, GBA testing is technically more challenging because of the nearby pseudogene, so long-range PCR followed by sequencing can be used.
- ✓ In ASMD, SMPD1 sequencing evaluates the coding region and flanking regions, but no sequencing assay covers every possible genomic variant.
- ✓ This is why deletion and duplication analysis matters.
- ✓ Current Lantern documentation describes CNV analysis in these pathways, including MLPA for GBA and defined CNV reporting rules for SMPD1.

# Biomarkers add a third diagnostic dimension



**Enzyme = function    Genetics = cause    Biomarker = biochemical context**

- ✓ Biomarkers add another dimension.
- ✓ In Gaucher, Lyso-GL1 is a highly informative disease biomarker.
- ✓ In ASMD, Lyso-SM reflects sphingomyelin storage and can support the diagnostic picture.
- ✓ Biomarkers should not be presented as replacements for enzyme or genetic testing. Their value is complementary: they can strengthen interpretation, help characterize disease burden and, in established disease, support longitudinal monitoring.

# What makes a strong reference laboratory?

Evidence-based criteria visible in modern specialist diagnostic programs



## ACCREDITATION

CLIA / CAP or equivalent



## VALIDATION

Assays + cut-offs



## QUALITY

QC + proficiency



## LOGISTICS

DBS + reliable TAT



## MOLECULAR

NGS + CNV



## REPORTING

Clear interpretation

### Selection principle

### Analytical quality + operational reliability + specialist expertise

- ✓ The public programs show the type of quality framework required: accredited laboratories, validated assays, documented quality control, rapid turnaround, reliable DBS logistics, molecular capability, CNV analysis where required, appropriate reporting and data protection for a sponsored program are essential.
- ✓ The laboratory should be able to integrate reflex testing rather than simply send back an isolated enzyme number.
- ✓ The goal is a diagnostic pathway, not a laboratory transaction.

# Global testing scale: what can we say confidently?



suspected symptomatic  
Pompe patients

57 countries

30,193

evaluable

723

Pompe diagnoses

283

GAA alterations

## Important limitation

No credible public source supports one cumulative global total for every Sanofi-sponsored Pompe + Gaucher + ASMD enzyme/genetic test since inception.

**Use published datasets ; do not extrapolate.**

- ✓ This is where scientific accuracy is particularly important.
- ✓ A 2024 Sanofi Genzyme-associated study evaluated 30,836 symptomatic people suspected of Pompe from 57 countries. Of 30,193 evaluable samples, 1,843 had low or borderline enzyme activity and 723 Pompe diagnoses were identified, with 283 different GAA alterations.
- ✓ In the Lantern Project from 2018 to 2021, 6,473 panel tests and 1,339 targeted tests were conducted, with 140 laboratory-confirmed Pompe diagnoses.
- ✓ A 2026 ASPHO report describes 681 individuals tested through the Lantern Project for Gaucher from October 2018 through December 2024.

# When should the pediatrician think beyond the common diagnoses?

SANOFI | RARE DISEASE DIAGNOSTICS



## POMPE

Hypotonia  
Proximal weakness  
± cardiomyopathy



## GAUCHER

Hepatosplenomegaly,  
anemia,  
thrombocytopenia  
Bone/systemic signs



## ASMD

Organomegaly  
Pulmonary disease  
Thrombocytopenia

**EARLY SUSPICION → LOW-BURDEN DBS TESTING → SPECIALIST CONFIRMATION**

- ✓ The final practical question is when to trigger testing.
- ✓ If a DBS result is abnormal, proceed rapidly to confirmation by Genetic analysis and biomarker assay,
- ✓ Rather than treating the DBS result as the final diagnosis.
- ✓ Genotype / phenotype correlation is suggested.

# Three messages to take home

01

**DBS**

ACCESS

02

**INTEGRATION**

CONFIDENCE

03

**EARLY SUSPICION**

ACTION

**A diagnostic service succeeds when it shortens the path from suspicion to the right diagnosis.**



- ✓ The key message is that DBS transformed rare-disease diagnosis from a geographically restricted specialist procedure into an accessible first-tier pathway.
- ✓ The technology evolved from single-enzyme assays to multiplex MS/MS, then to integrated biochemical, molecular and biomarker testing.
- ✓ For Pompe, GAA activity is the biochemical gateway and GAA genetics completes the diagnosis.
- ✓ For Gaucher and ASMD, parallel testing is particularly valuable.
- ✓ The most effective sponsored diagnostic service is therefore not simply a free test. It is a validated end-to-end pathway that reduces diagnostic delay and helps pediatricians identify children with treatable rare diseases earlier.

# Dried Blood Spot (DBS)

SANOFI | RARE DISEASE DIAGNOSTICS

01

## DBS For POMPE Disease



02

## DBS For Gaucher Disease



03

## DBS For ASMD



# تکمیل اطلاعات بیماران 1.

## LYSOSOMAL STORAGE DISEASES LABORATORY TEST REQUEST FORM



### PATIENT'S INFORMATION

Name, Surname **نام و نام خانوادگی با حروف لاتین**

Gender **جنسیت** Female ☐ زن Male ☐ مرد

ID No.  Date of Birth (Day/Month/Year)  Date of Sampling (Day/Month/Year)

Known Mutation in the family (If yes, Degree of Proximity / Name - Surname) Yes ☐ No ☐ Special Condition/Clinical Information

### EXAMINATION REQUESTED

☐ Fabry ☐ Gaucher & ASMD ☐ Chitotriosidase ☐ Lyso-GB-3  
☐ Pompe ☐ MPS Enzyme Panel ☐ Lyso-GB-1 ☐ Other:

### PATIENT'S LEGAL REPRESENTATIVE (Contact Information if the patient is under 18 years of age)

Name, Surname  ID No.  Phone Number

### DOCTOR'S DETAILS

Institution and Department   
 Doctor Name Surname

تاریخ تولد و نمونه  
گیری میلادی  
سال / ماه / روز



BIOHAZARD

It has been prepared for informing medical physicians only.

Complete the entire section about the patient information.

Be sure to fill each of the all blood circles carefully.

Aspirate blood from the front of the card only.

Absorb blood evenly into each of the circles.  
The front and back of the circles must be completely filled.

A repeat absorption process must not be performed  
in the circled on a dried card and avoid touching.

Do not switch to another without filling one circle.

Do not take the parts of the DBS kit apart.

Scan the QR code for Dried Blood  
Sampling video.



MAT-IR-2400001

اطلاعات  
بیمار

درج موتاسیون شناخته  
شده در خویشاوندان  
در صورت وجود سابقه

انتخاب نوع تست با  
توجه به درخواست  
پزشک

اطلاعات نماینده بیمار  
(بیماران زیر سن  
قانونی)

اطلاعات پزشک  
درخواست کننده تست  
شامل: نام و نام  
خانوادگی و تخصص و  
دپارتمان خدمت

# تکمیل اطلاعات بیماران 1.

هر فیلتر پیپر مخصوص بررسی یک بیماری (آنزیم) است

محل  
قرارگیری  
نمونه خون

**PATIENT INFORMATION AND CONSENT FORM**

This form is a declaration that I request that the analyzes specified in the field of rare diseases and/or on the above/first-front page be performed on myself and/or my child, that I give full permission, authorization and approval to the center with my free will in this regard, and that I fully understand the issues stated below.

I hereby consent to the processing of my personal data (Test Results) to be obtained during the study I have given and even during the study to be carried out in accordance with Article 5 and Article 6 of the Personal Data Protection Law No. 6698 ("PDPL") with this consent/request form I have given to my doctor/health institution/laboratory. I allow my doctor, the Health Institution and the laboratories where the test will be performed to share my personal and sensitive personal data with other third parties within the scope of Article 8 of the PDPL, "for the provision of services and/or development of services or medical research" related to my health.

This Consent Form also means that both my samples and analysis results may be de-identified and used for scientific research, test validation and training purposes. I understand that I can revoke this Consent Form at any time by contacting the relevant Laboratory and/or my Doctor/Health Institution. I understand and accept the rare risks that may arise in genetic studies, such as unsuitability of the material, use of drugs, cellular factors or failure to produce results due to technical reasons originating from the laboratory, and I also accept that false negative/positive results may be given, that the tests/examinations to be performed have a margin of error even if the relevant test/examination is performed accurately and that the results must be evaluated together with clinical findings.

By signing this document, I acknowledge that I have received, read and understood this information and consent form and that I have received the necessary explanations from my doctor. Please sign and write "I have read and understood".

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Name - Surname - Signature Patient



# Selected scientific references

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Key sources supporting the historical and methodological narrative

- Umapathysivam K, et al. Early DBS-based diagnosis of Pompe disease. 2001.
- Chamois NA, et al. DBS enzyme assays for Gaucher and Niemann–Pick disease. Early 2000s.
- Gelb MH, et al. Multiplex lysosomal enzyme activity measurement by tandem mass spectrometry. 2004.
- De Jesus VR, et al. Dried blood spots in lysosomal storage disorder screening and diagnosis.
- Sanofi Genzyme-associated international Pompe diagnostic experience; Human Mutation, 2024.
- Sanofi / Lantern Project: sponsored diagnostic testing pathway for Pompe, Gaucher and ASMD.
- Current Sanofi Rare Disease Specialty Testing Program materials: biomarkers and immunogenicity.
- Current Revvity / Lantern methodology: enzyme activity, GAA/GBA/SMPD1 sequencing and CNV.

Thank you for your attention  
for your shared commitment to improving patient outcomes



**Many Thanks for Your Attention**