CASE STUDY

BRCA Analysis: Expanding Global Access with the SOPHiA DDM™ Platform

BRCA mutations, pivotal in hereditary ovarian and breast cancers, are now recognized for their association with increased risks of prostate and pancreatic cancer. Since the landmark approval of Olaparib in 2014, PARP inhibitors (PARPi) have become the gold standard for treating these cancers.

However, meeting the rising demand for testing and analysis poses significant challenges, with the integration of NGS workflows into primary care still lacking. This case study explores *BRCA1* and *BRCA2* analysis on the SOPHiA DDM™ Platform, showcasing the potential of decentralization to expedite access to critical genetic insights.

SOPHiA GENETICS™

Highlights

- SOPHiA DDM™ Hereditary Cancer Solutions (HCS) and Homologous Recombination Solutions (HRD) are widely used and well-established NGS applications across the global SOPHiA DDM™ network.
- These solutions are well-equipped to accurately investigate *BRCA* status, offering streamlined end-to-end workflows and robust analytics capabilities.

Benefits

- A strategic collaboration between SOPHiA GENETICS and BioPharma can expedite the implementation and adoption of NGS workflows covering *BRCA* detection in healthcare institutions.
- The SOPHiA DDM™ network, particularly strong in the EMEA region, holds the potential to accelerate access to targeted therapeutics and clinical trials in this region.

Features

- Streamlined **sample-to-report** NGS workflows.
- **Decentralized and technology-agnostic SOPHiA DDM™ Platform**, with the potential to reduce turnaround time and enhance access to critical genetic insights.
- **Robust analytics** powered by proprietary algorithms and a vast repository of Real-World Data.
- Streamlined **implementation programs** (SOPHiA DDM™ MaxCare Program) tailored to simplify and accelerate the adoption of NGS workflows in healthcare Institutions.

DECODING RISK ASSOCIATED WITH *BRCA* MUTATIONS

Scope

Breast cancer genes *BRCA1* and *BRCA2* are the genes most commonly affected in hereditary forms of ovarian and breast cancers[1]. They are crucial in regulating cell proliferation and supporting normal tissue growth. Growing evidence further underscores the connection between *BRCA* mutations and an increased risk of prostate and pancreatic cancers[2].

BREAST CANCER

Breast cancer is the second most common cancer globally and a leading cause of female cancer deaths. The prevalence of germline *BRCA1* and *BRCA2* mutations is around 3%, rising to 15-20% in triple-negative breast cancer (TNBC) patients.

Those inheriting a harmful *BRCA1* variant have a 55%–72% risk of developing breast cancer by age 70–80, while *BRCA2* pathogenic variant carriers face a 45%–69% risk[3,4].

OVARIAN CANCER

Ovarian cancer is one of the most common gynecologic cancers with the highest mortality rate.

Women who inherit a harmful *BRCA1* variant face a 39%–44% risk of ovarian cancer by age 70–80, while those with a harmful *BRCA2* variant have an 11%–17% risk. Although these mutations are relatively rare in the general population (around 0.2-0.3%), they can surge to over 10% in groups with a family history of breast and ovarian cancers[5].

PROSTATE CANCER

Prostate cancer is the second most common type of cancer in men worldwide and is characterized by considerable heterogeneity. While most localized cases can be managed, some progress aggressively to metastasis with a median overall survival (OS) of only 18-36 months. Current risk stratification systems often lack precision in outcome prediction .

BRCA mutations are frequently linked to more aggressive disease and unfavorable outcomes. By age 75, *BRCA* carriers face a 21-27% risk of malignancy[1]. However, these mutations are relatively rare, present in only 1-3% or less of the patient population[2].

PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent type of pancreatic cancer and ranks as the seventh leading cause of cancer-related deaths globally. Today, less than 1 in 100 patients are predicted to survive for 5 years or more after diagnosis.

Germline *BRCA* mutations are detected in approximately 5-10% of familial PDAC cases and around 3% of sporadic PDAC cases.

For individuals carrying *BRCA2* mutations, the risk of malignancy is 3-4 times higher in comparison to non-carrier populations, whereas *BRCA1* mutation carriers may face a roughly 2-fold increased risk[7].

TABLE 1 | A snapshot of the prevalence and risk of *BRCA* mutations among different types of cancer.

1. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2023 Sep 21]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/
2. Pilarski R. The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. Am Soc Clin Oncol Educ Book. 2019;39:79-86. doi: 10.1200/EDBK_238977
3. Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clin Epidemiol. 2019;11:543-561. doi: 10.2147/CLEP.S206949
4. National Cancer Institute. BRCA Gene Mutations: Cancer Risk and Genetic Testing. Accessed on: October 2023. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet
5. Ataseven B, Tripon D, Rhiem K, et al. Prevalence of BRCA1 and BRCA2 Mutations in Patients with Primary Ovarian Cancer - Does the German Checklist for Detecting the Risk of Hereditary Breast and Ovarian Cancer Adequately Depict the Need for Consultation? Geburtshilfe Frauenheilkd. 2020;80(9):932-940. doi: 10.1055/a-1222-0042
6. Cancer Genome Atlas Research Network. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015;163(4):1011-25. doi: 10.1016/j.cell.2015.10.025
7. Lai E, Ziranu P, Spanu D, et al. BRCA-mutant pancreatic ductal adenocarcinoma. Br J Cancer. 2021;125(10):1321-1332. doi: 10.1038/s41416-021-01469-9

STANDARD OF CARE FOR THE TREATMENT OF *BRCA*-MUTATED CANCERS

Management

BRCA genes play a pivotal role in DNA repair processes, rendering tumors with *BRCA* mutations exceptionally vulnerable to anticancer drugs that induce DNA damage. If these DNA breaks go unaddressed, it can lead to genomic instability and cell death[8].

The discovery of the poly(ADP-ribose) polymerase (PARP) enzyme family and its role in DNA repair dates back to the early 1960s. Among this protein family, PARP1 stands out as the most well-recognized and established member. Its function as a **DNA break sensor**, binding to damaged sites and facilitating the recruitment of DNA repair proteins, was a groundbreaking discovery. By the 1980s, it became evident that PARP enzymes were not merely crucial for DNA repair but also that inhibiting them held the potential to amplify the cytotoxic effects of specific drugs[9].

The first PARP inhibitor (PARPi), 3-aminobenzamide, was discovered shortly after[8]. As of Q1 of 2024, several PARPi have been approved by the FDA for the management of *BRCA*-mutated cancers[8]:

Olaparib:

2014
First approved for the treatment of advanced ovarian cancer

2018
Olaparib became the first PARP inhibitor approved by the FDA for the treatment of *BRCA*-mutated and *HER2*-negative breast cancer

2019
Olaparib gained FDA approval for the indication of metastatic pancreatic cancer

Rucaparib and niraparib:

2016 and 2017
Both PARP inhibitors have been approved for the treatment of HRD-positive ovarian cancer, in 2016 and 2017, respectively

April 2020
Niraparib was approved as first-line monotherapy maintenance for platinum-responsive advanced ovarian cancer regardless of *BRCA* status

May 2020
Rucaparib was also approved for the treatment of *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC)

Talazoparib:

June 2023
In June 2023, in combination with enzalutamide (non-steroidal antiandrogen), talazoparib received approval for HRR-mutated mCRPC treatment

8. Drew Y. The development of PARP inhibitors in ovarian cancer: from bench to bedside. Br J Cancer. 2015;113 Suppl 1(Suppl 1):S3-9. doi: 10.1038/bjc.2015.394
9. Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol. 2017;18(10):610-621. doi: 10.1038/nrm.2017.53

THE IMPORTANCE OF EXPANDING ACCESS TO TIMELY *BRCA* ANALYSIS

Challenge

BRCA testing and analysis have assumed a pivotal role in clinical practice, driven by the emergence of FDA-approved PARPi. The importance of assessing its status cannot be overstated, as it empowers healthcare providers to make informed decisions, tailor treatment strategies, and ultimately enhance patient outcomes.

Yet, incorporating *BRCA* analysis workflows into primary care is not without its challenges. The surge in demand for such tests is compelling clinical practices to expand their screening capabilities. Simultaneously, they grapple with the multi-faceted task of deciphering actionable variants from the noise inherent to complex datasets[10].

These challenges are often intricate, spanning various stages of the testing process, including[9,11]:

- Precise analysis of 'noisy' data obtained from formalin-fixed paraffin-embedded (FFPE) tumor samples.
- Developing streamlined workflows that enable swift interpretation and real-time communication at the point of care.
- Navigating the complexities of implementing and scaling up efficient NGS workflows.
- Addressing the challenge of accessing timely bioinformatic analysis support.
- Filling the gaps in healthcare professionals' knowledge and training.

Tackling these challenges extends beyond proficiency; it's about optimizing time and resources. SOPHiA GENETICS addresses these issues through comprehensive training, streamlined implementation, and accelerated *BRCA* interpretation workflows with the decentralized SOPHiA DDM™ Platform.

10. Wallace AJ. New challenges for BRCA testing: a view from the diagnostic laboratory. Eur J Hum Genet. 2016;24 Suppl 1(Suppl 1):S10-8. doi: 10.1038/ejhg.2016.94
11. Pace LE, Tung N, Lee YS, et al. Challenges and Opportunities in Engaging Primary Care Providers in BRCA Testing: Results from the BFOR Study. J Gen Intern Med. 2022;37(8):1862-1869. doi: 10.1007/s11606-021-06970-8

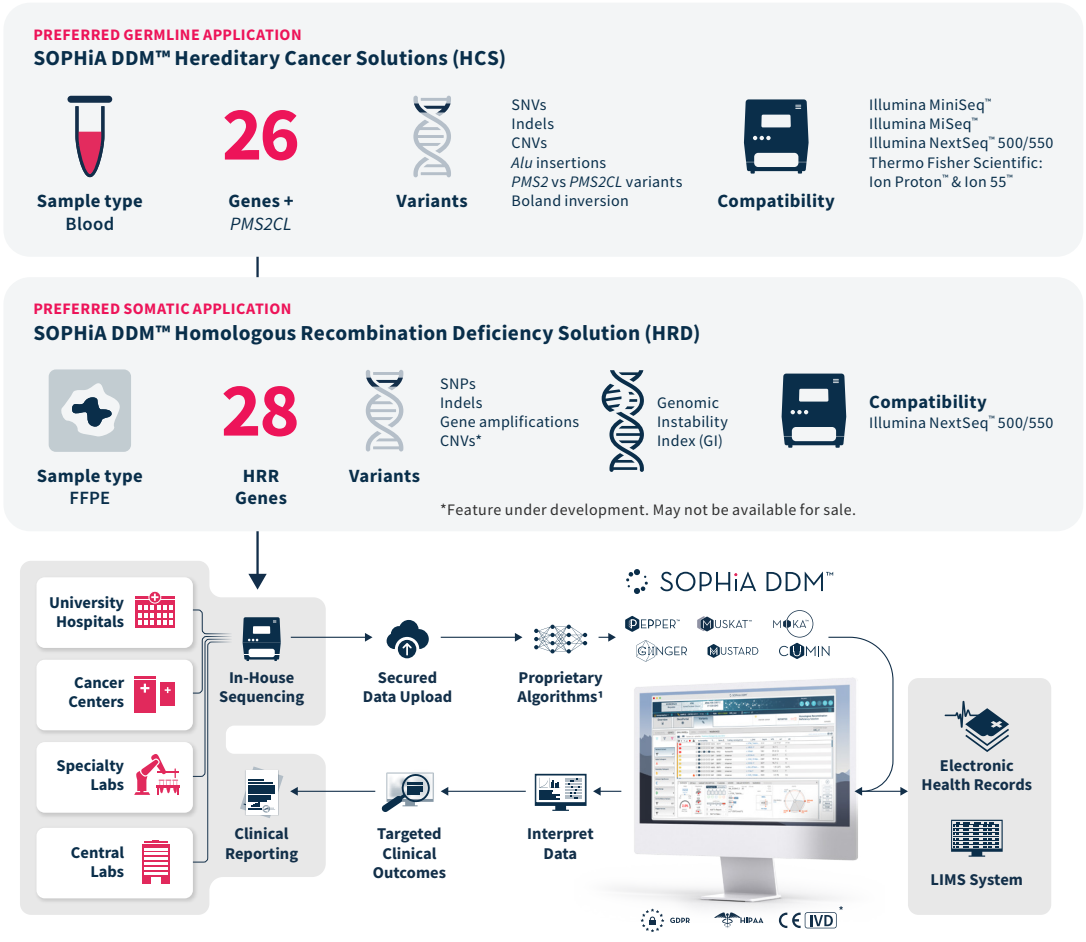
AN OVERVIEW OF THE SOPHiA DDM™ PLATFORM

Methods

The SOPHiA DDM™ Platform is a technology with a dynamic ecosystem, uniting a global community of interconnected users and relying on advanced analytical capabilities, secure decentralized solutions, and streamlined end-to-end workflows. Powered by machine learning and proprietary algorithms, our cloud-based platform standardizes, analyzes, and extracts comprehensive insights from complex NGS data.

As a flexible and scalable platform, SOPHiA DDM™ embraces a rapidly expanding global network of 750+ institutions and **1.5 million genomic profiles**, growing by more than 1,000 new profiles every day*. To further accelerate the adoption of NGS into clinical research and practice, we offer robust implementation and deployment programs supported by extensive training and verification. Since April 2018, our team completed over 480 successful programs across more than 270 institutions, reflecting our ongoing mission to democratize precision medicine.

*The number of institutions represents active customers who have generated revenue through the SOPHiA DDM™ platform usage or Alamut™ Visual Plus licenses as of September 30, 2022. The number of profiles refers to those analyzed from December 31, 2021, up to February 2024.



*Exclusively an accessory for SOPHiA DDM™Dx Hereditary Cancer Solution, SOPHiA DDM™ Dx RNAtarget Oncology Solution, SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution, SOPHiA DDM™ Dx Myeloid Solution, and SOPHiA DDM™ Dx Solid Tumor Solution.

Figure 1 | Streamlined sample-to-report workflows for the detection of germline and somatic *BRCA* mutations in the decentralized SOPHIA DDM™ Platform, gathering NGS data from healthcare institutions to foster collective and global intelligence.

A SNAPSHOT OF THE *BRCA* FOOTPRINT IN THE SOPHiA DDM™ PLATFORM

Footprint

To get a glimpse into the global utilization of our solutions and the *BRCA* status within the network, we analyzed samples processed through the SOPHiA DDM™ Platform over a **6-month period**. These figures offer a snapshot of our footprint. For more recent or extensive data insights, reach out to our team at biopharmasupport@sophiagenetics.com.

Over 6 months, the decentralized SOPHiA DDM™ Platform network analyzed more than **69,000 profiles** in **40+ countries** across the globe using germline and somatic applications encompassing *BRCA1* and *BRCA2* genes.

Within our global network, the EMEA region comprised **74%** of the analyses (over 51,000 profiles), while LATAM represented **11.9%** (over 8,200 profiles). This underlines the substantial adoption of decentralized testing and analytical approaches in these regions. Within EMEA, Turkey, Italy, and Spain reported the highest number of analyses, while in LATAM, Brazil, Colombia, and Argentina led the way.

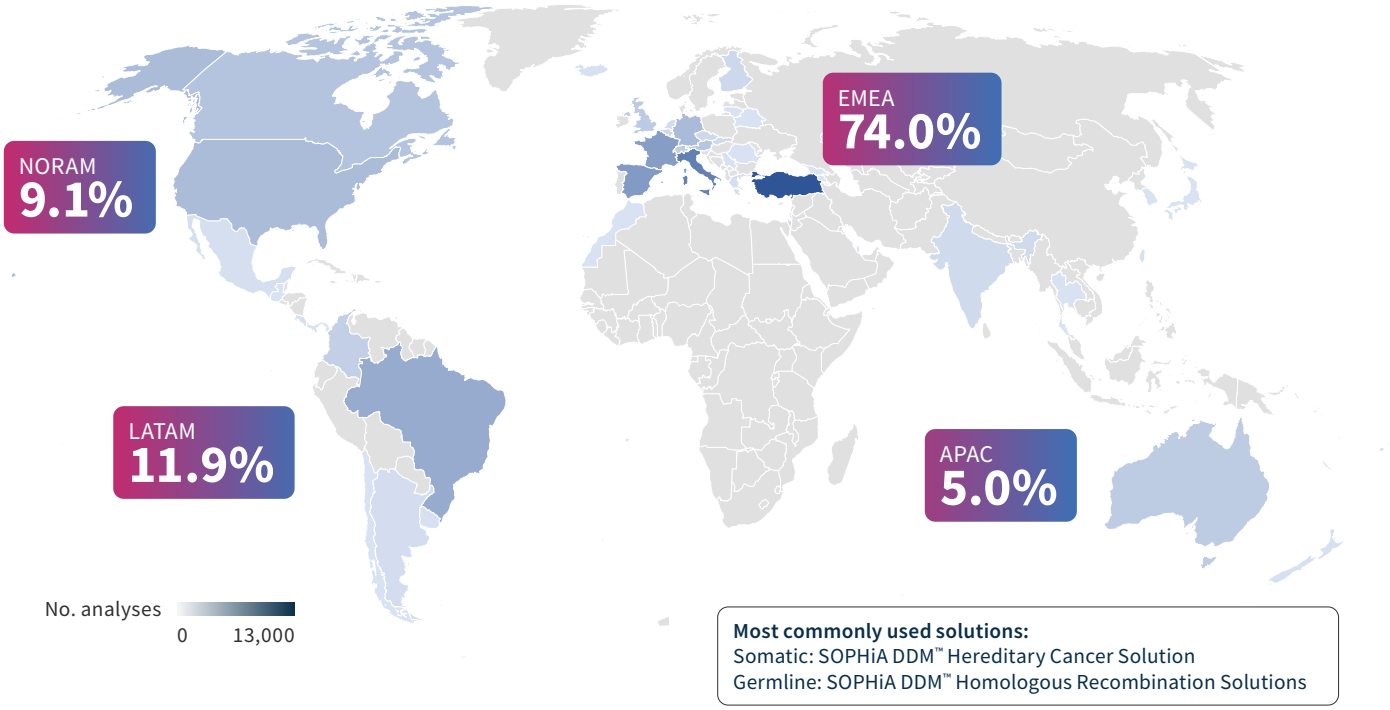


FIGURE 2 | A snapshot of global *BRCA1* and *BRCA2* gene analyses and the most commonly used solutions in the SOPHiA DDM™ Platform over a period of 6 months.

A COMPREHENSIVE LOOK AT *BRCA* FOOTPRINT IN THE SOPHiA DDM™ PLATFORM

Mutations

During the same 6-month period, a detailed examination of the Single Nucleotide Variants (SNVs) and Insertion-Deletions (Indels) detected via the SOPHiA DDM™ Platform unveiled a **marked prevalence of germline detection within the network**, driven by analyses using SOPHiA DDM™ HCS. Specifically, the total count of *BRCA1* and *BRCA2* mutations identified via germline solutions exceeded that of somatic solutions by 7-fold (DATA NOT SHOWN).

The ratio between **potentially pathogenic *BRCA* variants** (identified through BRCA Exchange - version 5912) and **variants of uncertain significance (VUS)** per institution was 1:50 in germline applications analyzed through the SOPHiA DDM™ Platform. Conversely, somatic applications showed a more diverse ratio due to their smaller footprint. Thus, for *BRCA1* and *BRCA2* this ratio was 1:6 and 1:4, respectively (FIGURE 3).

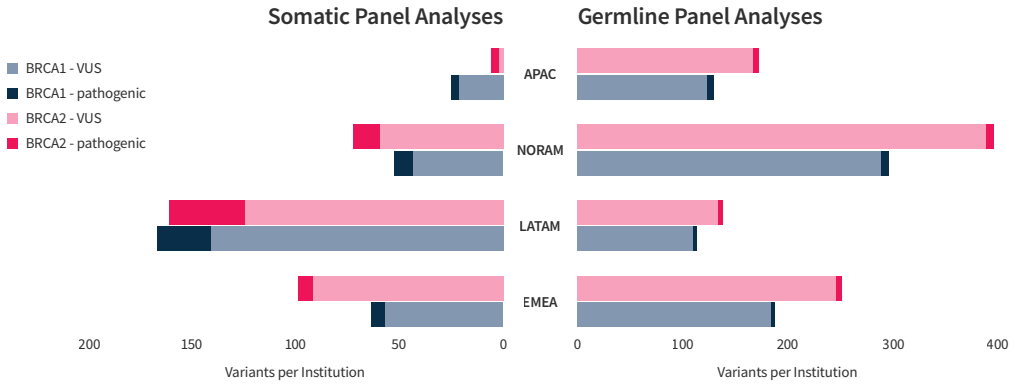


FIGURE 3 | Distribution of potentially pathogenic variants and variants of uncertain significance (VUS) normalized per institution and region for *BRCA1* and *BRCA2* analyzed in the SOPHiA DDM™ Platform from Q4 2021 to Q1 2022.

An in-depth examination of potentially pathogenic variants reveals a **notable predominance of frameshift mutations** in *BRCA1* and *BRCA2*, with only a few exceptions observed across diverse regions and application types. The average occurrence for this specific type of coding consequence stands at 53.5% for *BRCA1* and 78.6% for *BRCA2*, regardless of the application type employed. Following frameshifts, the most frequently observed mutations are nonsense mutations, with a median occurrence ranging from 17.5% to 37.8%, followed by missense mutations, with a median prevalence ranging from 2.2% to 5.7%.

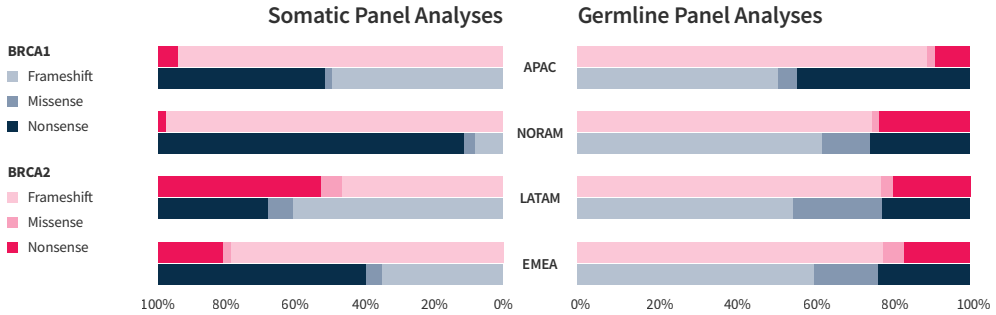


FIGURE 4 | Comparison between the relative abundance of the coding consequences found in potentially pathogenic variants of *BRCA1* and *BRCA2* in the SOPHiA DDM™ Platform from Q4 2021 to Q1 2022.

12. Cline MS, Liao RG, Parsons MT, et al. BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2. PLoS Genet. 2018;14(12):e1007752. doi: 10.1371/journal.pgen.1007752

KEY FINDINGS

Conclusion

- Over a 6-month period, the SOPHiA DDM™ Platform analyzed **69,000 profiles** using germline and somatic applications covering *BRCA* genes, with **74%** from the **EMEA** region.
- Germline applications, particularly SOPHiA DDM™ HCS, were the preferred applications used for *BRCA* variant detection.
- In germline applications, the ratio of **potentially pathogenic variants to VUS was 1:50**.
- **Frameshift** mutations were the most prevalent variant type detected by the SOPHiA DDM™ network.

OPPORTUNITIES TO EXPAND ACCESS TO STREAMLINED *BRCA* APPLICATIONS THROUGH THE SOPHiA DDM™ PLATFORM

Use cases

Timely access to genetic information is vital for managing the risks associated with *BRCA* mutations. However, the surge in demand often overwhelms centralized labs[13], hindering equitable access. Decentralizing testing and analysis offers a solution:

- **Enhanced accessibility:** Testing closer to patients, reducing shipping burdens.
- **Local processing and streamlined workflows:** Quicker turnaround times.
- **Scalability:** Flexible expansion to meet growing demands.
- **Equitable access:** Reducing disparities and engaging communities.

This decentralized model promotes collaboration and data sharing among testing centers, optimizing resources and providing tailored solutions. It fosters a more efficient genetic testing network integrated with centralized labs.

13. Donohue KE, Gooch C, Katz A, Wakelee J, Slavotinek A, Korf BR. Pitfalls and challenges in genetic test interpretation: An exploration of genetic professionals experience with interpretation of results. Clin Genet. 2021;99(5):638-649. doi: 10.1111/cge.13917

Expand access to PARPi by co-developing CDx applications

SOPHiA DDM™ HRD and HCS hold the potential to enhance global access to *BRCA* variant detection. Tailored for the decentralized SOPHiA DDM™ Platform, both solutions feature the CE-IVD label*, ensuring reliable and consistent analytical performance.

Leveraging SOPHiA GENETICS' global experience in genetic application implementation via the SOPHiA DDM™ MaxCare Program ensures strong and consistent performance, making adoption seamless across diverse markets and enhancing access and data harmonization.

Step by Step: MaxCare Program

Benefits:

- **Streamlined** implementation of NGS workflows
- Strategies **tailored** to the unique requirements and resources of **each institution**

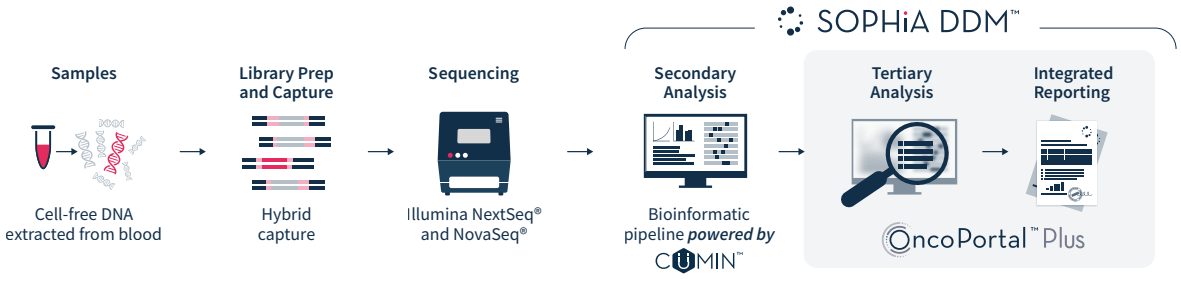
Learn more about the SOPHiA DDM™ MaxCare Program →

*SOPHiA DDM™ Dx Hereditary Cancer Solution and SOPHiA DDM™ Dx Homologous Recombination Deficiency Solution are available as CE-IVD products for In Vitro Diagnostic Use in Europe and Turkey. Information about products that may or may not be available in different countries and, if applicable, may or may not have received approval or market clearance by a governmental regulatory body for different indications for use. Please contact us at support@sophiagenetics.com to obtain the appropriate product information for your country of residence.

Expand access to *BRCA* analysis for emerging indications

While *BRCA* analysis is pivotal for breast and ovarian cancer, there's a pressing need to extend its application to pancreatic and prostate cancer.

Prostate cancer, especially when confined to bone metastasis, presents challenges with traditional biopsies. SOPHiA DDM™ applications, tailored for liquid biopsy*, offer minimally invasive insights into disease progression and facilitate effective disease management[14].



Learn more about the SOPHiA DDM™ for Liquid Biopsy →

*SOPHiA DDM™ for Liquid Biopsy is a product in development and may not be available for sale. SOPHiA DDM™ for Liquid Biopsy is for Research Use Only and not intended for use in diagnostic, therapeutic, or treatment purposes unless specified otherwise.

14. Ionescu F, Zhang J, Wang L. Clinical Applications of Liquid Biopsy in Prostate Cancer: From Screening to Predictive Biomarker. Cancers (Basel). 2022;14(7):1728. doi: 10.3390/cancers14071728

Take the next step in your precision oncology journey

If you are seeking to harness our expertise, tap into our collaborative network, and explore Real-World Data to propel your precision oncology research, we invite you to reach out to our team. Together, we can transform the landscape of cancer care and drive impactful advancements.

GET IN TOUCH >

SOPHiA GENETICS™

Democratizing Data-Driven Medicine, Together

About us

SOPHiA GENETICS (Nasdaq: SOPH) is a software company dedicated to establishing the practice of data-driven medicine as the standard of care and for life sciences research. It is the creator of the SOPHiA DDM™ Platform, a cloud-native platform capable of analyzing data and generating insights from complex multimodal data sets and different diagnostic modalities. The SOPHiA DDM™ Platform and related applications, modules and services are currently used by a broad network of hospital, laboratory, and biopharma institutions globally.

Want to know more?

Contact us at: biopharmasupport@sophiagenetics.com