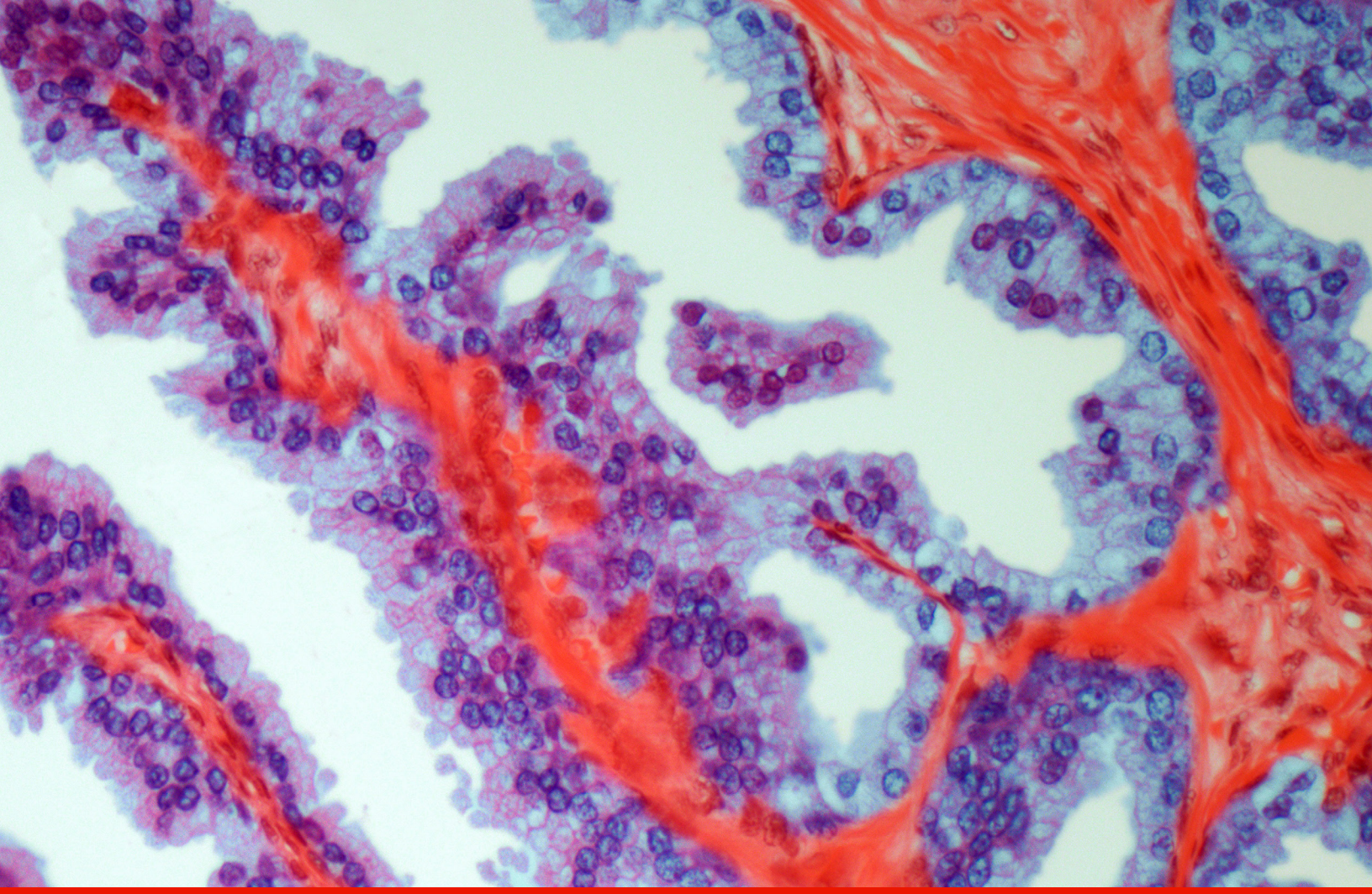

Prostate Cancer Biomarker Testing Sample Requirements, Methods, and Opportunities

J&J
Precision Medicine

Biomarker-informed decision-making in prostate cancer improves outcomes[1]

Multiple alterations contribute to the evolution of prostate cancer[1,2]	
Androgen signaling	*Androgen receptor (AR)* amplification, *AR* mutations, *AR* variants, *GATA2, FOXA1, SRCs, MAGE-11*
DNA repair system and oncosuppressors	Homologous recombination repair (HRR) genes (*BRCA1, BRCA2, ATM, CHEK2, PALB2, RAD51D*), *MSH2, CHD1, TP53, Rb, PTEN, SPOP*
Prostate-specific antigens and transcription factors	*TMPRSS2:ERG, ETV1, ERF, NKX3.1, PCA3, PSMA*
Oncogenes and growth factor receptors	*Myc, EGFR, KGFR, IGFR*
Biomarker-informed disease management has improved outcomes in prostate cancer[1]	

In *BRCA1/2*-mutated prostate cancer, PARP inhibitors have been shown to hinder DNA repair mechanisms, effectively delaying disease progression in advanced cases[3–5]

Did you know?

In a study of patients with prostate cancer post radical prostatectomy, **biomarker testing results changed management recommendations for 39% of patients, significantly reducing two-year PSA recurrence rates[6,7]***

Guidelines recommend molecular testing in prostate cancer[6,8,9*†]

Guidelines recommend molecular testing for prostate cancer to[6,8,9*†]:

- **Understand the risk of developing prostate cancer**
- **Identify prognostic markers**
- **Determine potential targeted therapies**

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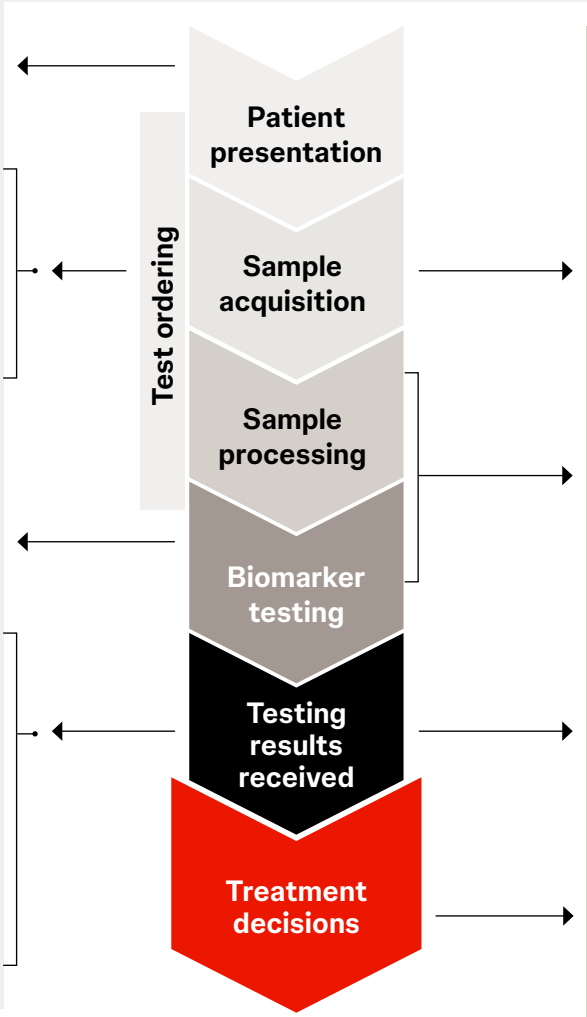
†AUA/SUO Advanced Prostate Cancer Guideline discusses molecular testing for metastatic disease.[9]

Successful biomarker testing relies on adherence to best practices[6,8,10,11]*



MDT communication is essential for timely and accurate diagnosis and management of patients with prostate cancer[12–14]

Opportunity to optimize

Early consultation with MDT members may help ensure that adequate samples are acquired and appropriately prepared for the intended testing procedure[12–14]

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†Dependent on cancer type and procedure.[13,14]

Tissue biopsy should be performed when advanced prostate cancer is suspected and no prior histologic confirmation[9]

Biopsy is recommended for primary tumors, or metastatic sites when feasible, which allows for histological confirmation and molecular evaluation to help guide treatment decisions for patients with advanced prostate cancer[9]

Sampling considerations

- Can be performed through a **systematic and/or targeted** imaging approaches (MRI-TRUS) with improved diagnostic accuracy[15–17]
- Tissue can be taken from **primary or metastatic sites**[18,19]
- **Nonbone metastases are preferred** for biopsy due to higher tumor yield and feasibility[18]
- **Account for the amount of tissue required** for molecular pathology[14]

Analysis considerations

- Analysis can be done on **archived or freshly collected tissue**[14,18]
- Availability of **sufficient genomic material** for comprehensivetesting[18,20]
- Tumor heterogeneity may lead to **false negatives**[18,21,22]

Opportunity to optimize

Rapid on-site evaluation (ROSE) helps ensure optimal sample collection and improve diagnostic efficiency[13]

Liquid biopsy can be used when tissue biopsy is inadequate or inappropriate[22]

When to consider liquid biopsy?

- As a complement to tissue testing[22]
- Where tissue biopsy is not possible or sufficient[22]
- When only archival tissue DNA is available[22]

Sampling considerations

- Is **minimally invasive** and can be easily accessed in comparison with tumor tissue[22,23]
- Provides **an overview of both primary and metastatic sites**[22]
- Sample quality is **dependent on shedding of circulating tumor markers**[22,24]
- **Collection during progression is preferred** to maximize diagnostic yield[6*]

Analysis considerations

- **Repeat testing is feasible** due to minimally invasive nature of liquid biopsy[22]
- Analysis is **not limited by tumor heterogeneity** as it may be for tissue biopsy[22]
- **May be associated with false negatives** if samples are below limit of detection[18]

Opportunity to optimize

Regardless of biopsy method, it is important to obtain sufficient and appropriate samples for molecular analysis[18]

Biomarker tests may be ordered at initial diagnosis and/or when disease progresses[6,8]*

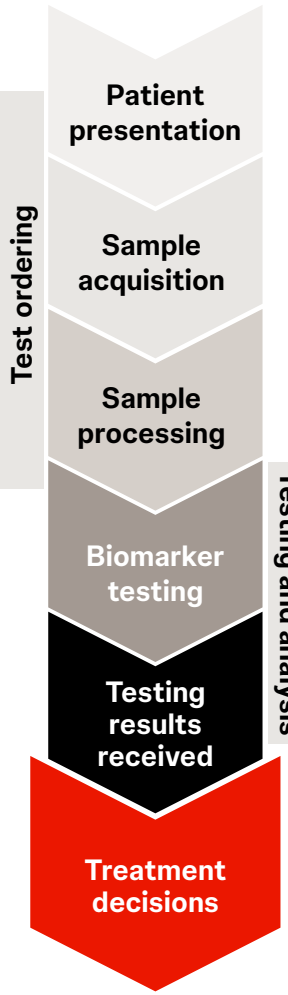
When to order biomarker testing

Germline and somatic testing: At initial diagnosis

To understand genetic predisposition, inform prognosis, facilitate biomarker-directed treatment selection, and determine eligibility for clinical trials[6,8]*

Somatic testing: At time of progression

To monitor treatment response, inform prognosis and aid in treatment decision-making[6,8]*



A good biomarker test should:

Be scientifically rigorous

- **Strong, evidence-based support** for accuracy with which a test measures
  - The target biomarker(s) (analytic validity)[25,26]
  - A patient's clinical status (clinical validity)[26,27]
  - The risks and benefits (clinical utility)[26,27]
- Tests should be **sensitive, specific, accurate, and precise** to effectively detect alterations[25,26]
- Tests should be performed on **samples with documented and optimized collection, fixation, processing, and storage** for biomarker testing[25,26]

Provide valuable, actionable, and timely information

- Results should be **actionable** and/or **inform clinical decision-making**[26]
- **Clear protocols exist** for interpreting test results, including protocols for negative results[26]
- **Optimal turnaround times** allowing results to impact treatment decisions[27]

What makes a good biomarker test?

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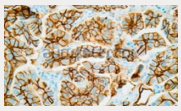
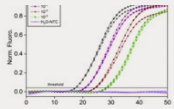
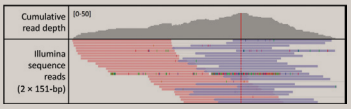
Actionable biomarkers in prostate cancer that can inform treatment decisions may be detected by different assays with unique capabilities[28–34]

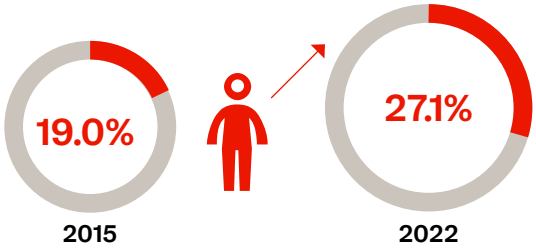
	Single-biomarker test[32,35]		Broad-based panel[32,35]
Test type	**Immunohistochemistry (IHC)[28,29]**	**Polymerase chain reaction (PCR)[29–31]**	**Next-generation sequencing (NGS)[29,32–34]**
			
Alteration type(s) detected	Overexpression/ amplification, protein expression	Single-nucleotide variant (SNV), copy number variant (CNV), insertions-deletions (indels), known gene fusions	SNV, CNV, indels, genomic rearrangements
Actionable biomarkers detected	MLH1, MSH2, MSH6, PMS2	MSI, *MLH1, MSH2, MSH6, PMS2*	MSI, TMB, *MLH1, MSH2, MSH6, PMS2, ATM, BRCA1, BRCA2, CDK12, CHEK2, PALB2, FANCA, NBN*

Images adapted from: Kipf E, Schlenker F, Borst N, et al. Advanced minimal residual disease monitoring for acute lymphoblastic leukemia with multiplex mediator probe PCR. *J Mol Diagn*. 2022;24(1):57–68; Watson CM, Nadat F, Ahmed S, et al. Identification of a novel MAGT1 mutation supports a diagnosis of XMEN disease. *Genes Immun*. 2022;23(2):66–72. https://creativecommons.org/licenses/by/4.0/

Opportunity to optimize

NGS is an efficient way to test for multiple alterations[29,32]

NGS testing in prostate cancer is increasing and helps inform treatment decisions[36]



Overall rates of **NGS testing** in the US increased from **19.0% in 2015 to 27.1% in 2022** for males with metastatic prostate cancer[36]

Advantages[36–38]	Challenges[37]
• **Fast, accurate, and comprehensive** assessment to guide treatment decisions • Efficiently identifies more actionable alterations, leading to **improved outcomes and reduced cost compared with single-gene testing**	• Access to **fresh/frozen tissue is preferred**, but not always feasible • **Routine sampling of metastases is not always performed**

NGS testing provides fast, accurate, and comprehensive assessment to guide treatment decisions[37,38]

Disparities and barriers in prostate cancer impact biomarker testing access[36,39–41]

Although overall rates of NGS testing in the US are increasing, disparities and barriers to testing remain[39]

- Cost of testing
- Accessibility and availability of approved tests
- Race and socioeconomic status

Individuals are less likely to undergo NGS testing if they[36,40]:

- Are of Black or Hispanic/Latino race
- Are of low socioeconomic status
- Are on government insurance
- Live in the Western US

Opportunity to optimize

Be mindful of potential barriers that may impact molecular testing in appropriate patients to ensure they receive the treatment they need[36,39,40]

MDTs collaborate to interpret test results and recommend a course of action[39,41]

Results reporting considerations

- Receive test result in EHR vs PDF/fax for rapid and more accurate access[8,10]*
- Specify biomarker presence, and positive or negative result, in the report[10]
- Indicate targeted therapy eligibility from biomarker testing results[8,10]* (eg, NGS for HRR alterations may indicate PARPis)

Opportunities for laboratories and HCPs to collaborate for optimal testing and reporting

- Work toward optimal testing and reporting practices[8,10]*
- Support HCP awareness of ordering the appropriate test[12,42]
- Improve communication within the MDT across the entire patient journey[39,42]

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Prostate cancer biomarker testing is rapidly evolving in key areas of active research including[43–45]:

Use of liquid biopsy for detection of minimum residual disease (MRD)[46]

MRD refers to a small number of remaining tumor cells during or after treatment and **indicates tumor persistence and potential progression.** NGS is a primary MRD detection method[47]

Liquid biopsy is emerging with the potential to detect MRD based on the presence of ctDNA and CTCs[46]

Circulating tumor cells (CTCs)

- CTCs are derived from solid tumors[46]
- Analysis before salvage lymph node dissection may indicate metastasis[46,48]
- Analysis before and after radiotherapy may detect CTCs in patients with high-risk non-metastatic prostate cancer[46,49]

Circulating tumor DNA (ctDNA)

- Hypermethylation of *ZNF660* promotor may be used in differentiating indolent from aggressive cancers[46,50]
- Low allele fraction and technical or biological interference may affect the reliability of the results[46]

Emerging biomarkers with increasing interest in miRNAs[51]

miRNAs may have diagnostic, prognostic, and predictive value[51]

- miRNAs may be diagnostic, prognostic, and predictive biomarkers with **particular promise in diagnosis of early disease**[51]
- Ratios of circulating miRNAs **may differentiate between localized prostate cancer and BPH** to help avoid unnecessary biopsies[51,52]

AR and *TP53* are potential prognostic biomarkers[53,54]

- ***AR* alterations** are associated with the development of CRPC and may be potential prognostic biomarkers for prostate cancer[54–56]
- Mutations leading to a **loss of function in tumor suppressor genes like *TP53*** may be associated with progression[53,57]

Co-mutations may predict response in patient subgroups[58,59]

- Individuals with ***BRCA* mutations co-occurring with *TP53* mutations** have worse response to PARPi than those with only *BRCA* mutations[58,59]
- **Co-mutation of *BRCA1* with *PARP1*** may confer PARPi resistance[58,60]

Prostate cancer biomarker testing is rapidly evolving in key areas of active research including[43–45] (cont'd):

The diagnostic, prognostic, and predictive value of epigenetic biomarkers[53,61–63]

Diagnosis of prostate cancer

- DNA methylation assays may be **effective in diagnosing early-stage cancers** because epigenetic alterations occur early in tumorigenesis and can be specific to both tissue and cancer type[62]

Understanding prognosis

- Testing for hypermethylation at biopsy (eg, *ZNF660*) may **enable risk stratification** and help **avoid overtreatment of indolent prostate cancer**[46,50]
- Hypermethylation of *GSTP1, APC, RARB*, and *PITX2* is associated **with an elevated risk of recurrence and/or mortality**[53,64–67]

Predictive treatment response

- Cell-free DNA (cfDNA) methylation may help **identify resistance mechanisms**, such as in neuroendocrine prostate cancer[61,68]

Taking an integrated "multi-omic" approach to biomarker analysis[69,70]

Integrative multi-omics analysis

- Combining genomics, transcriptomics, and epigenomics enhances the ability to identify patients likely to benefit from current therapies, revealing critical mutational signatures linked to treatment response and early diagnosis[69,70]
- **DNA methylation and mutational signatures**
  - May help identify cancer cells, enabling **early diagnosis and reducing overdiagnosis**[63,69]
  - Effectively detect high-grade prostate cancer[63,69]
- **Transcriptomic and proteomic insights**
  - Differentially expressed genes, miRNAs, and proteomic signatures show promise as **diagnostic and prognostic biomarkers** for prostate cancer[51,69]

Data integration and AI in cancer management

- Advances in **high-throughput technologies**, combined with bioinformatics and AI, **may improve data analysis, enhance diagnostic accuracy**, and aid in managing prostate cancer through better risk stratification[53]

Biomarker testing informs prostate cancer treatment decisions[6,9,71*]

Understanding the molecular profile of prostate cancer can **inform precision medicine approaches** that are tailored to the patient's tumor[6,72*]

Adequate biopsy **sample quantity and quality and use of appropriate tests** is necessary for optimal identification of actionable prostate cancer biomarkers[6,12,13*]

MDT communication helps ensure best practices are followed for sample collection, analysis, and interpretation of test results[12,13,39,41]

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AI, artificial intelligence; *APC, adenomatous polyposis coli*; AR, androgen receptor; *ATM, ataxia-telangiectasia mutated*; BPH, benign prostatic hyperplasia; AUA, American Urological Association; *BRCA, breast cancer gene*; *CDK12, cyclin-dependent kinase 12*; cfDNA, cell-free DNA; *CHD1, chromodomain helicase DNA-binding protein 1*; *CHEK2, checkpoint kinase 2*; CNV, copy number variant; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; DNA, deoxyribonucleic acid; *EGFR, epidermal growth factor*; EHR, electronic health record; *ERF, ETS2 repressor factor*; *ETV1, ETS variant transcription factor*; *FANCA, FA complement group A; FOXA1, forkhead box A1; GATA2, GATA-binding protein 2; GSTP1, glutathione S-transferase P1*; HCP, healthcare provider; HRR, homologous recombination repair; *IGFR, insulin-like growth factor 1 receptor*; IHC, immunohistochemistry; indel, insertion-deletion; *KGFR, keratin growth factor receptor*; *MAGE-11, melanoma antigen gene protein-A11*; mCRPC, metastatic castration-resistant prostate cancer; MDT, multidisciplinary team; miRNA, microribonucleic acid; *MLH1, MuTL homolog 1*; MRD, minimum residual disease; MRI, magnetic resonance imaging; *MSH2/6, MutS homolog2/6*; MSI, microsatellite instability; *Myc, myelocytomatosis virus oncogene*; *NBN, nibrin gene*; NCCN, National Comprehensive Cancer Network® (NCCN®); NGS, next-generation sequencing; *NKX3.1, NK3 homeobox 1*; *PALB2, partner and localizer of BRCA2; PARP1, poly-ADP ribose polymerase-1*; PARPi, poly-ADP ribose polymerase inhibitor; *PCA3, prostate cancer antigen 3*; PCR, polymerase chain reaction; PDF, portable document format; *PITX2, paired-like homeodomain transcription factor 2; PMS2, postmeiotic segregation increased 2*; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; *PTEN, phosphatase tensin homolog; RAD51D, RAD51 homolog D; RARB, retinoic acid receptor beta; RB, retinoblastoma;* ROSE, rapid on-site evaluation; SNV, single-nucleotide variant; *SPOP, speckle-type POZ protein; SRC, steroid receptor coactivator*; SUO, Society of Urologic Oncology; TMB, tumor mutational burden; *TMPRSS2:ERG, transmembrane protease, serine 2:ETS-related gene*; TP53, tumor protein p53; TRUS, transrectal ultrasound; US, United States; *ZNF660, zinc finger protein 660*.

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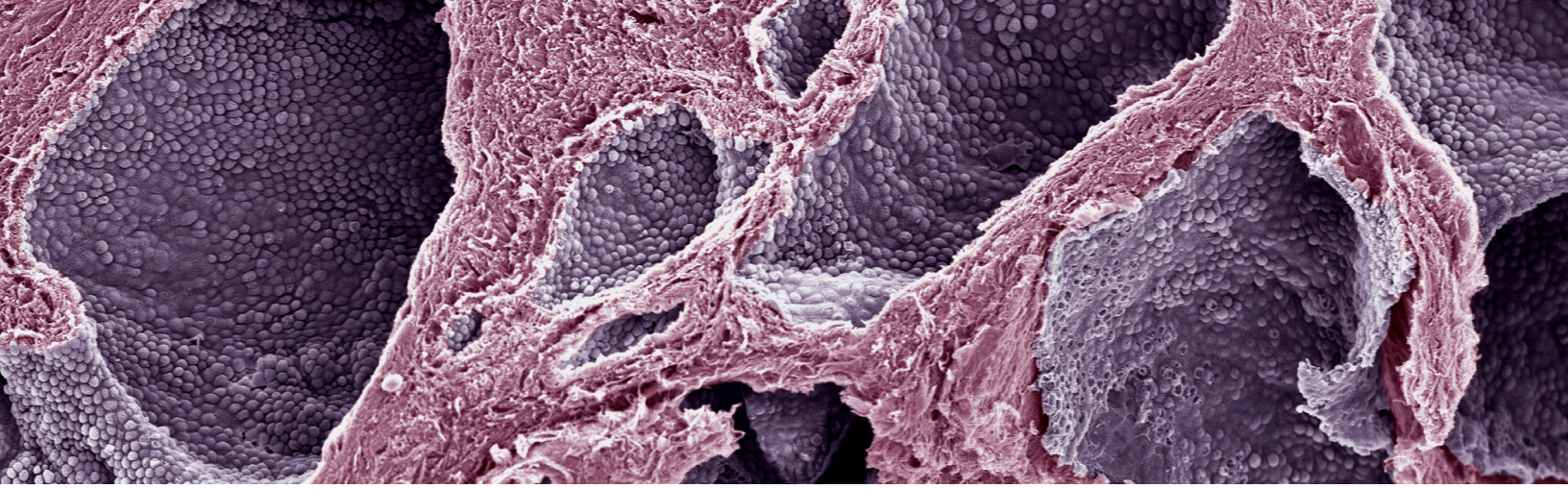

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