Urology Hereditary Genetics

Prostate Cancer

Gene Panel:* *ATM, BRCA1, BRCA2, CHEK2, EPCAM, FANCA, HOXB13, MITF, MLH1, MSH2, MSH6, PALB2, PMS2, TP53, BRIP1, RAD51C, RAD51D, NBN

Germline BRCA1 and BRCA2 pathogenic variants have been associated with increased risk for prostate cancer, with the association being strongest for advanced or metastatic prostate cancer. In addition, BRCA1, BRCA2, and ATM pathogenic variant rates are highest in patients with metastatic prostate cancer.

The risk of developing prostate cancer in individuals with Lynch syndrome (*i.e.*, men with pathogenic variants in EPCAM, MLH1, MSH2, MSH6, or PMS2) increases from 11.2% in the general population to approximately 30% with a mean age of onset of 59 to 69 years (reported for MLH1, MSH2, and MSH6). A meta-analysis of studies found men with Lynch syndrome were 2.13 to 3.67 times more likely to develop prostate cancer. In addition, 73% of prostate cancers in men with Lynch syndrome were found to exhibit deficient mismatch repair with immunohistochemistry (IHC) results consistent with the germline variant, suggesting the prostate cancer was a result of Lynch syndrome.

In Table 1 below, a strong history of prostate cancer consists of:

- Known germline variants in genes for Lynch syndrome (EPCAM, MLH1, MSH2, MSH6, and PMS2) and homologous recombination genes (ATM, BRCA1, BRCA2, CHEK2, and PALB2).
- Brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at less than 60 years or who died from prostate cancer.
- Ashkenazi Jewish ancestry.
- Greater than three cancers on the same side of the family, especially those diagnosed at 50 years or younger including bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer.

Table 1. Germline Testing Recommendations (NCCN)

Risk Group	Clinical/Pathologic Features			Germline Testing
Very Low	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density <0.15 ng/mL/g			Recommended if family history positive or intraductal histology
Low	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Recommended if family history positive or intraductal histology
Intermediate	Has no high- or very high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10-20 mg/mL	Favorable Intermediate	• 1 IRF AND • Grade Group 1 or 2 AND • <50% biopsy cores positive	Recommended if family history positive or intraductal histology
		Unfavorable Intermediate	• 2 or 3 IRFs AND/OR • Grade Group 3 AND/OR • ≥50% biopsy cores positive	Recommended if family history positive or intraductal histology
High	• T3a OR • Grade Group 4 or 5 OR • PSA >20 ng/mL			Recommended
Very High	• T3b-T4 OR • Primary Gleason pattern 5 OR • ≥4 cores with Grade Group 4 or 5			Recommended

The National Comprehensive Cancer Network (NCCN) recommends germline genetic testing for all men with high-risk, very-high-risk, regional, or metastatic prostate cancer.

Germline genetic testing of the homologous recombination genes ATM, BRCA1, BRCA2, CHEK2, and PALB2 with the addition of FANCA and RAD51D should be considered for men with castration-resistant prostate cancer (CRPC) and conventional imaging studies positive for metastases.

Management

BRCA1 and BRCA2 pathogenic variant carriers have an increased risk of prostate cancer before 65 years of age. Prostate cancer in men with BRCA2 pathogenic variants occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, prostate cancer screening starting at age 45 is recommended for BRCA2 carriers and considered for BRCA1 carriers. Also, it is reasonable for men with germline BRCA1 and BRCA2 pathogenic variants to consider PSA screening at age 40 and subsequent annual screening.

ATM, BRCA1, BRCA2, CHEK2, FANCA, PALB2, RAD51D: Information regarding pathogenic variants in these homologous recombination DNA repair genes may be used for genetic counseling (individual and family), evaluating early use of platinum chemotherapy, and assessing eligibility for clinical trials (e.g., PARP inhibitors). Variants in ATM, BRCA1, BRCA2, CHEK2, or PALB2 and/or a strong family history should be referred to a genetic counselor to assess for hereditary breast and ovarian cancer (HBOC) and be managed accordingly (individual and family).

References:

1. Surveillance, Epidemiology, and End Results Program. Cancer Stat Fact Sheets. Accessed February 8, 2021. Available at http://seer.cancer.gov/.
2. National Cancer Institute. Accessed February 8, 2021. Available at http://www.cancer.gov/.
3. NCCN Prostate Cancer Guidelines, Version 1.2019. Available at http://www.nccn.org/.
4. NCCN Prostate Cancer Early Detection Guidelines, Version 1.2019. Available at http://www.nccn.org/.
5. NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 3.2019. Available at http://www.nccn.org/.
6. NCCN Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2018. Available at http://www.nccn.org/.

Renal Cancer

Gene Panel: BAP1, EPCAM, FH, FLCN, MET, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SDHD, TSC1, TSC2, VHL

Studies from Memorial Sloan Kettering Cancer Center have found that 16% of patients with advanced renal cell carcinoma carried a pathogenic germline DNA variant. Most of the patients in this study had clear cell renal cell carcinoma, the most common subtype of kidney cancer. In this large group of patients, approximately 14% had a germline variant. Moreover, up to 20% of patients with non-clear cell renal cell carcinoma carried a germline variant.

Germline Testing Recommendations

Renal cell carcinoma (RCC) with clear cell histology, if any of the following are met:

- Diagnosis at less than 50 years
- One or more close relatives with clear cell RCC
- RCC with papillary type 1, type 2, collecting duct, tubulopapillary, or Birt-Hogg-Dubé (BHD)-related histology
- Urothelial carcinoma (or transitional cell carcinoma) and two additional cases of any Lynch syndrome-related (LS) cancer in the same person or in relatives
- RCC and two additional Cowden syndrome criteria in the same person
- Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person

Tumors associated with LS: Colorectal adenocarcinoma, endometrial adenocarcinoma, urothelial carcinoma (ureter and renal collecting ducts), gastric cancer, ovarian cancer, small bowel cancer, glioblastoma, sebaceous adenocarcinoma, biliary tract cancer, pancreatic cancer.

Table 2. Management

Gene(s)	Syndrome	Renal Characteristics	Renal Management
BAP1	BAP1 tumor predisposition syndrome	• Increased risk for ccRCC • Median age of diagnosis is 47 years • More aggressive and likely to metastasize • Decreased length of survival • Distinct histology	• Genetic counseling • Surveillance: If abdominal MRI, consider evaluation of peritoneum and pleura • Treated in usual manner
VHL	Von Hippel-Lindau (VHL)	• Pathogenic variants in VHL are the most common cause of familial and sporadic RCC • ccRCC occurs in 70% of affected by age 60 • Leading cause of mortality in VHL syndrome	• Genetic counseling • Abdominal ultrasound after age 16 and evaluate suspicious lesions by CT/MRI
MET	Hereditary papillary renal carcinoma (HPRC)	• Linked to hereditary papillary renal carcinoma (HRPC) • High-risk for type 1 papillary • Most with HRPC will develop tumors in lifetime	• Genetic counseling • Encourage discussion regarding CT/MRI/ Ultrasound
FH	Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	• Associated with solitary and aggressive tumors of type 2 papillary • Occur in up to 16% of patients with HLRCC • Median age of diagnosis is 44 years	• Genetic counseling • Yearly abdominal MRI is recommended • Evaluate suspicious renal lesions by CT
FLCN	Brit-Hogg-Dubé (BHD)	• Increased risk for renal tumors, typically bilateral and multifocal, and slow growing	• Genetic counseling
TSC1, TSC2	Tuberous sclerosis complex (TSC)	• Renal disease 2nd cause of early death in TSC • RCC occurs in 2%-5% of TSC with median age of diagnosis of 28-30 years	• Genetic counseling • Abdominal MRI every one to three years • Access renal function and BP annually
PTEN, SDHB, SDHC, SDHD	Cowden syndrome	• Lifetime risk for RCC is ~35% with a starting age in the 40s • Predominant histology is papillary renal cell carcinoma	• Genetic counseling • Biennial renal CT/MRI beginning at age 40 • With family history: Consider screening five to ten years prior to the youngest diagnosis in family
EPCAM, MLH1, MSH2, MSH6, PMS2	Lynch syndrome (LS)	• Increased risk of transitional carcinomas of the ureter, renal pelvis, and bladder	• Genetic counseling • Consider annual urine analysis beginning between are 30 and 35

Medical Diagnostic Laboratories (MDL), offers the following hereditary genetics tests for renal cancer and prostate cancer.

References:

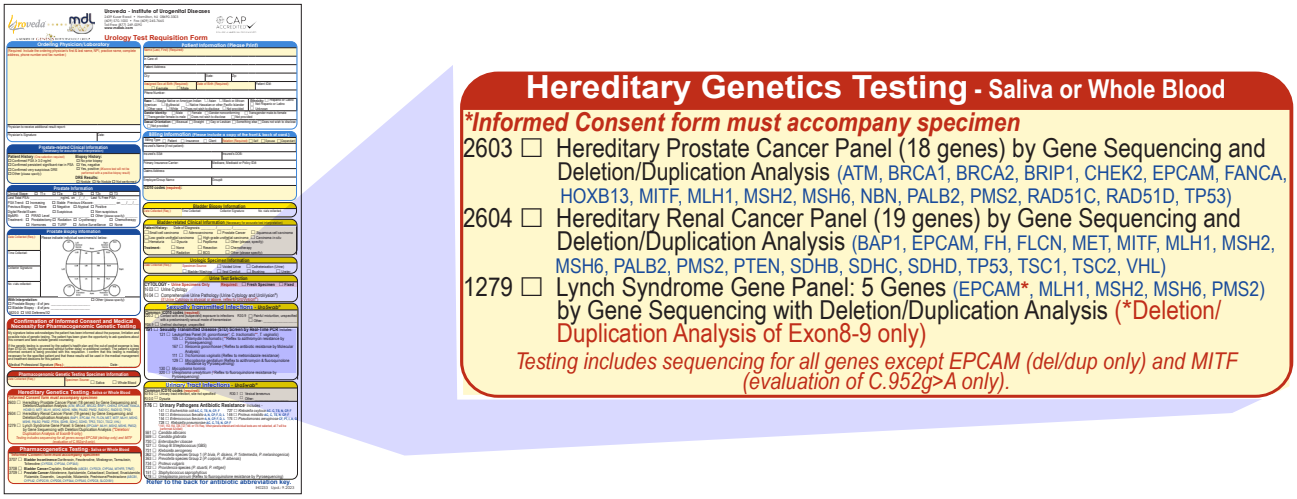

Figure 1: MDL's Hereditary Genetic tests for urology.

1. Surveillance, Epidemiology, and End Results Program. Cancer Stat Fact Sheets. Accessed March 15, 2019. Available at http://seer.cancer.gov/.
2. National Cancer Institute. Accessed February 8, 2021. Available at http://www.cancer.gov/.
3. ACMG Practice Guidelines. Genetics in Medicine, 17:1, January 2015.
4. JAMA Oncol. July 5, 2018.
5. Gene Reviews. Accessed February 8, 2021. Available at http://www.ncbi.nlm.nih.gov/.
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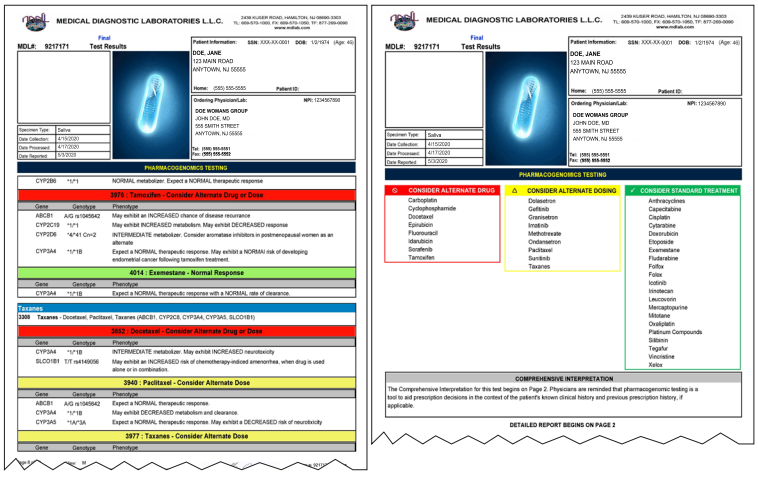
Pharmacogenomics

Pharmacogenomics is the study of the influence of genetic variation on drug response in patients. This variability can lead to therapeutic failure or severe toxicity. Pharmacogenomic testing provides a means for physicians to consider which medications may be appropriate for a particular patient before ever actually writing a prescription. It also allows physicians to consider alternate medications, more effectively, in a situation where the patient is not responding as expected to a particular treatment. Pharmacogenomics can determine which drugs and drug combinations are optimal for each individual's unique genetic makeup to ensure maximum efficacy with minimal adverse effects. This valuable information can assist physicians in prescribing treatment for urinary incontinence, bladder cancer, and prostate cancer. MDL's Pharmacogenomic testing can determine how your patient will metabolize seventeen frontline drugs, including popular incontinence drugs and popular anti-neoplastics (**Table 3**).

Table 3. MDL Pharmacogenomic tests available for Urology.

	Test No.	Drug
Bladder Incontinence	4035	Darifenacin
	4036	Fesoterodine
	4037	Mirabegron
	4038	Tamsulosin
	3983	Tolterodine
Bladder Cancer	3828	Cisplatin
	4039	Erdafitinib
Prostate Cancer	4040	Abiraterone
	4041	Apalutamide
	4042	Cabazitaxel
	3852	Docetaxel
	4043	Enzalutamide
	4044	Flutamide
	4045	Goserelin
	4046	Leuprolide
	4047	Nilutamide
	3950	Prednisone/ Prednisolone

- *MDL Pharmacogenomic tests are available on saliva or whole blood.*



There are many enzymes that perform drug degradation, such as members of the Cytochrome P450 family, ion channels that regulate the flow of chemicals into and out of a cell, enzymes that 'tag' drugs with specific moieties for excretion, and so on. These enzymes vary genetically in the population, and this genetic variation often causes functional variation, as well. Although the majority of patients will respond predictably to the standard dose and regimen of most drugs, some patients do not. While one person may be typical of the population average and maintain the expected dose level of a drug, another may rapidly metabolize the drug and so fail to maintain a steady-state of drug. While yet another may metabolize the drug too slowly, allowing the levels to rise into concentrations that may be toxic. An unexpected response may lead to a drug being ineffective or hyper-effective, and this may be potentially very dangerous for the patient.

Specimen Collection

Pharmacogenomic testing can be performed from a noninvasive saliva specimen. Simply ensure that the patient has not eaten for a half-hour and that they rinse out their mouth just before providing a 2mL saliva sample in the tube provided. The tube does not need any special storage or shipping conditions. Testing can also be performed on whole blood submitted in either an ACD (solution A) or EDTA blood collection vial. The specimen is sent to Medical Diagnostic Laboratories (MDL) where DNA is extracted and analyzed using state-of-the-art technology called Next Generation Sequencing, sometimes referred to as deep sequencing, to build a library of the genes of interest.

Result Report

MDL's Pharmacogenomic result reports group each drug into one of three categories: Expect a "Normal Response" (Green Box), Consider an "Alternate Dose" (Yellow Box), and Consider an "Alternate Drug or Dose" (Red Box). Note that we do not make prescribing decisions on your behalf, these are recommendations, not proscriptive statements. For example, a drug can be Red Boxed for a variety of reasons from, possible cardiac effects to simple likely weight gained. Only the Physician can know whether this represents a true risk to the particular patient, or not. Pharmacogenomic testing takes much of the risk out of the picture, allowing the use of an individual's genetic data to help physicians tailor their prescribing to an individual patient.

References

1. Roses AD. 2004. Pharmacogenetics and drug development: the path to safer and more effective drugs. *Nat Rev Genet* 5(9): 645-656.
2. Relling MV, Evans WE. 2015. Pharmacogenomics in the clinic. *Nature* 526(7573):343-50
3. Alagoz O, Durham D, Kasirajan K. 2016. Cost effectiveness of one-time genetic testing to minimize adverse drug reactions. *Pharmacogenomics J* 16(2):129-136.
4. Daly AK. Pharmacogenetics: a general review on progress to date. *Br Med Bull* 124(1): 65-79, 2017.