

# Review of Cancer Risk Susceptibility and Drug Response in Consumer Genomic Services

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## Background

In the last several years, a variety of genetic tests have become available directly to consumers for both specific condition determination and genome-wide assessment. Genome-wide testing services genotype 600,000 – 1 million variants or SNPs (single nucleotide polymorphisms), the specific locations of possible mutation. These data may then be applied to predict overall risk susceptibility to health conditions and response to pharmaceuticals.

## Cancer conditions reviewed in Consumer Genomic Services

The five leading genome-wide services review health risk susceptibility for twenty-two cancer conditions (Figure 1).

Figure 1

### Consumer genomic service coverage of cancer conditions

Cancer condition	23andMe	MyHeritage	23andMe	MyHeritage	23andMe	MyHeritage
1. Cancer, Basal Cell Carcinoma	X	X	X	X	X	X
2. Cancer, Bladder	X	X	X	X	X	X
3. Cancer, Brain (Glioma)	X	X	X	X	X	X
4. Cancer, Breast BRCA Mutations (selected)	X	X	X	X	X	X
5. Cancer, Breast	X	X	X	X	X	X
6. Cancer, Breast Risk Modifiers	X	X	X	X	X	X
7. Cancer, Colorectal	X	X	X	X	X	X
8. Cancer, Esophageal	X	X	X	X	X	X
9. Cancer, Gastric from H. pylori	X	X	X	X	X	X
10. Cancer, Larynx	X	X	X	X	X	X
11. Cancer, Leukemia	X	X	X	X	X	X
12. Cancer, Lung	X	X	X	X	X	X
13. Cancer, Ovarian	X	X	X	X	X	X
14. Cancer, Pancreatic	X	X	X	X	X	X
15. Cancer, Prostate	X	X	X	X	X	X
16. Cancer, Stomach	X	X	X	X	X	X
17. Cancer, Testicular	X	X	X	X	X	X
18. Cancer, Thyroid	X	X	X	X	X	X
19. Cancer, Uterine	X	X	X	X	X	X
20. Cancer, Vulvar	X	X	X	X	X	X
21. Cancer, Vaginal	X	X	X	X	X	X
22. Cancer, Cervical	X	X	X	X	X	X

Sources:  
<https://www.23andme.com/health>  
<http://www.23andme.com/health-watch>  
<http://www.23andme.com/health-watch>  
<http://www.23andme.com/health-watch>  
<http://www.23andme.com/health-watch>  
<http://www.23andme.com/health-watch>

Legend:  
 2 23andMe  
 D deCODEme  
 N Navigenics  
 PG Pathway Genomics  
 GE Gene Essence

## Overview of Multigenic Risk Assessment

Determining carrier status may be straightforward, but applying genomics to complex common disease conditions is more challenging. There are thousands of GWAS (genome-wide association studies) linking one or more variants with disease. Numerous variants may be associated with a particular disease, for example, 34 variants in 22 loci in Prostate Cancer (Figure 2). Different companies have different criteria for selecting underlying research studies which leads to different loci and variants being included in their analyses. Questions arise as to which are the most important variants, whether all variants should be included and how equal weighting, and how to derive a quantitative composite risk score for the overall condition.<sup>1</sup> There is yet to be scientific agreement on these topics. In the interim, the important variants may be identified by the number of companies reviewing the variant, the P-value of the variant's association strength (P-values below 5x10<sup>-8</sup> are desirable), and the quality of the cited studies.

Figure 2

Side-by-side comparison of loci, genes, and variants reviewed for Prostate Cancer  
 Rows highlighted to improve readability, grouped by locus/genie

Locus	Gene	Variant	D	N	PG	P-value
2p15	EHEP1	rs2710646	8			n/a
2p15	EHEP1	rs2710646	8			8 x 10 <sup>-14</sup>
2p21	SLC22A3	rs1020754	4			n/a
3p12.1	SLC22A3	rs8660753	11			3 x 10 <sup>-14</sup>
4q24	TET2	rs10934853	9			3 x 10 <sup>-18</sup>
5p13	TERF	rs401681	18			7 x 10 <sup>-14</sup>
6p25.3	SLC22A3	rs3964554	11			6 x 10 <sup>-18</sup>
7	JAZF1	rs1048657	17			2 x 10 <sup>-14</sup>
10q21.3	LMTK2	rs6466557	11			2 x 10 <sup>-14</sup>
11p21	NKX3.1	rs1512268	4			3 x 10 <sup>-18</sup>
12p24	NKX3.1	rs1096928	1			n/a
16q24 region 1	rs1447295	6	20	2,3,5,6,14,15,16,18,20,22		2 x 10 <sup>-14</sup>
16q24 region 2	rs6983561	n/a				n/a
16q24 region 2	rs1050543	6		3,6,10,13,19,22		n/a
16q24 region 2	rs18901979	6		3,5,10,13,19,22		1 x 10 <sup>-14</sup>
16q24 region 2	rs1815777	n/a				n/a
16q24 region 2	rs6983267	20	20	3,10,20,21,22		9 x 10 <sup>-13</sup>
16q24.21	rs620681	9				n/a
16q24.21	rs620681	n/a				n/a
16q24.21	rs18902104	9				n/a
16q24.21	rs18902104	n/a				n/a
10q11.23	MSMB	rs1093994	17			7 x 10 <sup>-13</sup>
10q26.13	CTBP2	rs4962415	17			2 x 10 <sup>-17</sup>
11p15.1	IGF2B2	rs7127900	4			3 x 10 <sup>-13</sup>
11q13	rs7931342	n/a				2 x 10 <sup>-17</sup>
11q13	rs10896448	17	17			9 x 10 <sup>-17</sup>
17q12	HNF1B	rs7501939	7			2 x 10 <sup>-17</sup>
17q12	TCF2	rs430799	7		7.22	1 x 10 <sup>-11</sup>
17q24.3	rs1859962	n/a			7.22	2 x 10 <sup>-11</sup>
19q13.2	rs18102476	9				2 x 10 <sup>-11</sup>
19q13.32	KLK2LK3	rs2755839	11			2 x 10 <sup>-18</sup>
22q13.1	TNRC8	rs9823117	n/a			5 x 10 <sup>-17</sup>
22q13.2	rs5759167	4				6 x 10 <sup>-18</sup>
22q13.2	rs5759167	4				4 x 10 <sup>-17</sup>

Legend:  
 D deCODEme  
 N Navigenics  
 23andMe  
 PG Pathway Genomics

References cited by consumer genomic companies:  
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## Unified Genomic Reports: Health Risk and Drug Response

It is now starting to be possible to have a patient's genomic profile available to review health condition risk and predict drug response. Figures 3-6 provide an example of the variants that are currently being assessed in ovarian, prostate, pancreatic, and lung cancer, including the real genotyping data of a sample patient, and how the information might be interpreted. Ovarian cancer and pancreatic cancer are more sparsely covered than prostate cancer.

Figure 3

Drug(s) <sup>1</sup>	Chromosome <sup>2</sup>	Gene(s) <sup>1</sup>	Variant <sup>1</sup>	Mutation Allele <sup>1</sup>	Data from Patient #1 <sup>3</sup>	Potential Interpret. <sup>4</sup>	Ref. <sup>5</sup>
<b>Ovarian cancer risk susceptibility</b>							
BRCA1	17q21.31	BRCA1	rs2032582	n/a	n/a	n/a	1.3
BRCA2	13q12.2	BRCA2	rs11361	G	AG	less efficacious	2
BRCA2	13q12.2	BRCA2	rs11361	G	GG	less efficacious	2
<b>Ovarian neoplasm drug response</b>							
docetaxel, paclitaxel	17q21.31	BRCA1	rs2032582	n/a	n/a	n/a	1.3
docetaxel, paclitaxel	17q21.31	BRCA1	rs2032582	n/a	n/a	n/a	1.3
docetaxel, paclitaxel	17q21.31	BRCA1	rs2032582	n/a	n/a	n/a	1.3

References:  
 1. Ojamaa AA, et al. Nat Genet. 2009 Sep 20;41(9):938-44.  
 2. Kiviniemi M, et al. Pharmacogenomics J. 2010 Feb;10(1):54-61.  
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Figure 4

Prostate cancer risk susceptibility  
 Rows highlighted to improve readability, grouped by locus/genie

Locus or Gene <sup>1</sup>	Variant <sup>1</sup>	P-value <sup>2</sup>	Cos. Cov <sup>3</sup>	Mutation Allele <sup>1</sup>	Data from Patient #1 <sup>3</sup>	Potential Interpret. <sup>4</sup>	OR <sup>5</sup>	RR <sup>6</sup>	
8p11	rs2710646	n/a	D	C	CC	higher risk	1	0.95	
8p11	rs2710646	n/a	D	C	CC	higher risk	1	0.95	
2p15	rs1020754	n/a	D	C	AA	lower risk	1	1.03	
3p12.1	rs2690753	3 x 10 <sup>-8</sup>	D,PG	T	CT	higher risk	1.06	1.17	
3p12.1	rs10934853	3 x 10 <sup>-10</sup>	D	C	AA	lower risk	1	0.99	
4q24	rs7679673	3 x 10 <sup>-14</sup>	D	C	AC	higher risk	1.17	1.17	
5p13	rs401681	7 x 10 <sup>-17</sup>	D,PG	T	CC	lower risk	1.06	1.06	
6p25.3	rs3964554	2 x 10 <sup>-18</sup>	D,PG	T	CT	higher risk	1.06	1.06	
7	JAZF1	rs1048657	2 x 10 <sup>-14</sup>	D,N,PG	G	AA	lower risk	1	1
10q21.3	LMTK2	rs6466557	2 x 10 <sup>-14</sup>	D,PG	T	TT	higher risk	0.9	0.9
11p21	NKX3.1	rs1512268	3 x 10 <sup>-18</sup>	D	G	GG	higher risk	0.86	0.86
12p24	NKX3.1	rs1096928	1						
16q24 region 1	rs1447295	n/a	D	T	TT	higher risk	1.09	1.09	
16q24 region 2	rs1447295	2 x 10 <sup>-14</sup>	D,N,2,PG	A	CC	lower risk	1	1	
16q24 region 2	rs6983561	n/a	PG	C	AA	lower risk	1	0.98	
16q24 region 2	rs1050543	n/a	D,2	G	CC	lower risk	1	0.98	
16q24 region 2	rs18901979	1 x 10 <sup>-12</sup>	N	A	CC	lower risk	1	1	
16q24 region 2	rs1815777	n/a	2	G	AA	lower risk	0.98	0.98	
16q24.21	rs620681	9 x 10 <sup>-13</sup>	D,N,2,PG	G	GT	higher risk	1.26	1.09	
16q24.21	rs620681	n/a	D	T	CC	lower risk	1	0.94	
16q24.21	rs18902104	n/a	D	T	CC	lower risk	1	0.94	
10q11.23	MSMB	rs1093994	n/a	PG	T	GT	higher risk	1.15	1.03
10q26.13	CTBP2	rs4962415	17 x 10 <sup>-13</sup>	D,PG	T	CT	higher risk	1.03	1.03
11p15.1	IGF2B2	rs7127900	2 x 10 <sup>-17</sup>	N,PG	C	TT	lower risk	1	1
11q13	rs7931342	3 x 10 <sup>-18</sup>	D	G	AG	higher risk	1	1.12	
11q13	rs7931342	3 x 10 <sup>-18</sup>	D	G	AG	higher risk	0.73	1.12	
11q13.2	rs10896448	2 x 10 <sup>-17</sup>	D,N	G	AA	lower risk	1	1.42	
HNF1B	rs7501939	9 x 10 <sup>-17</sup>	PG	C	CC	higher risk	1.42	1	
TCF2	rs430799	1 x 10 <sup>-11</sup>	D,N,2	A	CC	lower risk	1	1	
17q24.3	rs1859962	2 x 10 <sup>-16</sup>	D,N,2	G	TT	lower risk	1	1	
19q13.2	rs18102476	2 x 10 <sup>-11</sup>	D	T	CT	higher risk	0.99	0.92	
KLK2L3	rs2755839	2 x 10 <sup>-18</sup>	D	AG	AG	higher risk	0.92	0.92	
TNRC8	rs9823117	5 x 10 <sup>-17</sup>	PG	C	TT	lower risk	1	1.14	
22q13.2	rs5759167	6 x 10 <sup>-18</sup>	D,2	A	GG	lower risk	1	1.14	
NDT11	rs5945572	4 x 10 <sup>-13</sup>	D,PG	A	GG	lower risk	1	1	

Legend:  
 D deCODEme  
 N Navigenics  
 23andMe  
 PG Pathway Genomics

## Prostate neoplasm drug response

Chromosome <sup>1</sup>	Gene <sup>1</sup>	Variant <sup>1</sup>	Mutation Allele <sup>1</sup>	Data from Patient #1 <sup>3</sup>	Potential Interpret. <sup>4</sup>	Ref. <sup>5</sup>
chr2:108361240	SULT1C2	rs1420467	G	CG	less efficacious	1
chr6:35461501	PPAR-D	rs6922548	G	AA	efficacious	1
chr6:35470503	PPAR-D	rs7769719	G	AG	less efficacious	1
chr6:3547784	PPAR-D	rs1833322	C	TT	efficacious	1
chr6:35486756	PPAR-D	rs2016520	C	TT	efficacious	1
chr6:35502988	PPAR-D	rs3734254	T	TT	less efficacious	1
chr10:73439513	CHST3	rs4148943	T	TT	less efficacious	1
chr10:73440123	CHST3	rs4148947	T	CC	efficacious	1
chr10:73442768	CHST3	rs730720	C	TT	efficacious	1
chr10:73443020	CHST3	rs12418	G	AA	efficacious	1

Drug toxicity for: docetaxel, thalidomide	Chromosome <sup>1</sup>	Gene <sup>1</sup>	Variant <sup>1</sup>	Mutation Allele <sup>1</sup>	Data from Patient #1 <sup>3</sup>	Potential Interpret. <sup>4</sup>	Ref. <sup>5</sup>
chr1:47051762	CYP4B1	rs4648467	T	CC	efficacious	1	
chr2:38151707	CYP1B1	rs1056836	G	CG	less efficacious	2	
chr8:18302650	NAT2	rs1799931	G	GG	less efficacious	1	
chr10:73439596	CHST3	rs4148945	T	TT	less efficacious	1	
chr10:73441712	CHST3	rs4148950	G	AA	efficacious	1	
chr10:73442020	CHST3	rs1871459	A	AA	efficacious	1	
chr13:102495729	SLC10A2	rs2301159	A	GG	efficacious	1	
chr16:16159100	ABOC6	rs2238472	C	TT	efficacious	1	
chr16:88140624	SPG7	rs2292954	A	AG	less efficacious	1	
chr16:88147829	SPG7	rs132660	C	CC	less efficacious	1	
chrX7:1751558	ATP7A	rs2227291	G	CG	less efficacious	1	

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Figure 5

Pancreatic cancer risk susceptibility (Pancreatic Neoplasm Drug Response: Figure 6)

Locus <sup>1</sup>	Gene(s) <sup>1</sup>	Variant <sup>1</sup>	P-value <sup>2</sup>	Mutation Allele <sup>1</sup>	Data from Patient #1 <sup>3</sup>	Odds Ratio <sup>4</sup>	Potential Interpret. <sup>4</sup>	Ref. <sup>5</sup>
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