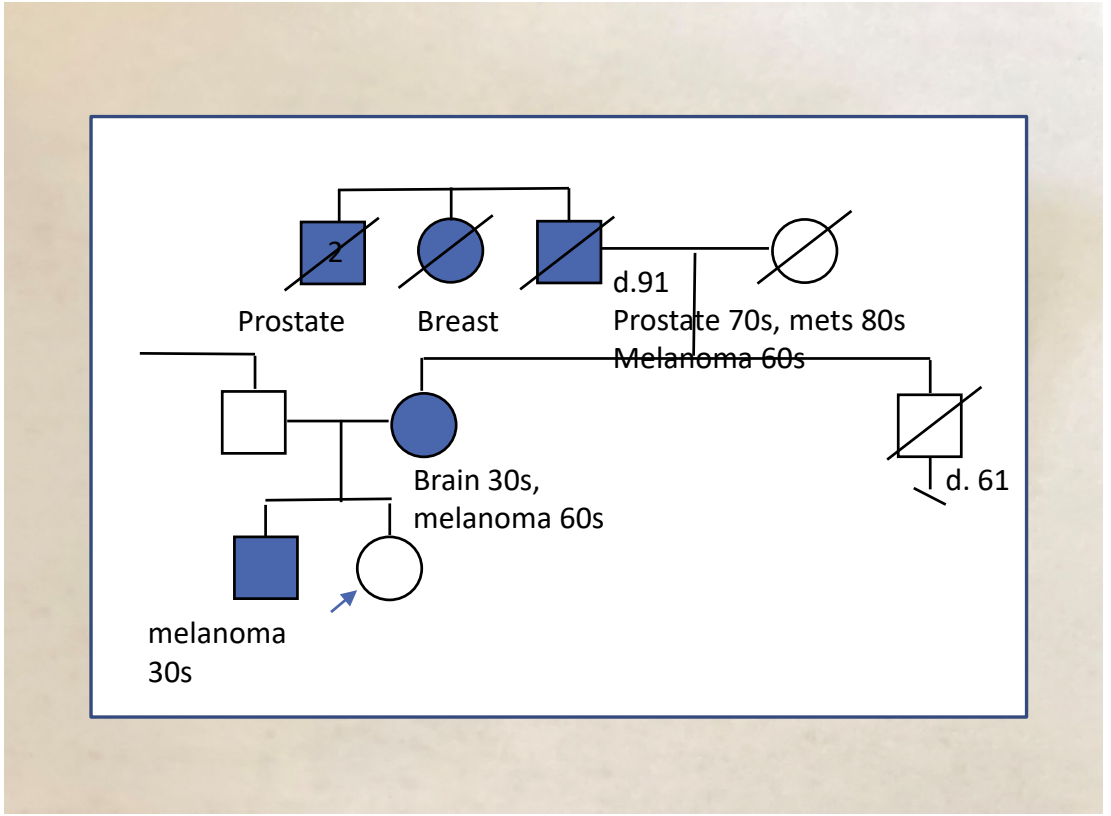
Does reduced penetrance = reduced patient impact? The report & beyond.

Cristi Radford, MS, CGC



Journey 1:

11/19/2018
Test Ordered

Apr 29, 2019, 9:10 AM

I'm on call. Everything ok

Yes. Grabbing a coffee and calling to check-in

Ok. Can call when off.

Report: 153 pages

Summary of Health Results > Clinical

Clinical Results

Some genes in your genome are associated with disorders that are severe but may not manifest until long after birth, sometimes not until later in adulthood. When variants are detected in such genes, it is important to discuss this result with a healthcare provider to determine next steps. These can include additional clinical exams to be able to catch early signs of a disease that may otherwise be overlooked. Sometimes, action can be taken to prevent the disorder from occurring, or to alter in some way its natural progression. We looked at genes associated with the most common genetic disorders. In addition, we examined a number of positions in other genes where well-known variants that occasionally result in disease can occur.

For a list of genes and positions tested please see the link in the Technical Note.

Very Important ▼▼▼

ORGAN HEALTH

This grouping covers a range of conditions involving (but not limited to) the following organs: lung, bone, kidney, liver, eye, ear, nose, throat, blood, skin, hair, and teeth. Therefore, it is possible to learn of a genetic susceptibility to a variety of conditions. Knowing this information can help your healthcare providers tailor your health plan and may influence your lifestyle choices.

Multiple Endocrine Neoplasia

WHAT IT MEANS

You have a genetic variant that is known to be associated with an increased risk to develop multiple endocrine neoplasia. This finding is considered significant by the ACMG because there are actions you can take to reduce your risk for serious disease.

GENE(S) & VARIANT(S)

- RET (NM_020975)
- c.1998G>T (p.Lys666Asn)
- Heterozygous
- Likely pathogenic

RECOMMENDATIONS

- Discuss results with your physician(s). Medical intervention may be indicated.
- Genetic Counseling is strongly recommended.
- Share this information with at-risk relatives. They may benefit from genetic testing.
- Immediate Action Recommended.

Clinical Results

Very Important ▼▼▼

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- Genetic Counseling is strongly recommended.
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INTERPRETATION

RET c.1998G>T (p.Lys666Asn) is a likely pathogenic variant associated with autosomal dominant multiple endocrine neoplasia (MEN), and more specifically medullary thyroid carcinoma (MTC). This variant has been reported in at least 11 unrelated affected individuals (Jaber 2016, Mazza 2016, Boichard 2012, Lebeault 2017, Yehia 2018, Xu 2016) and segregated with disease in 1 individual from 1 family (Xu 2016). Most affected individuals presented with medullary thyroid carcinoma with variable age of onset, all of which were reported in adulthood. Some family members, carriers for this variant, were also reported as asymptomatic, indicating a possible lower penetrance and/or a mild phenotype for this variant. In vitro functional study showed that this variant increases RET kinase activity (Mazza 2010). Other nucleotide changes affecting the same amino acid position (p.Lys666Glu) have been reported in affected individuals. This variant was identified in 7/129112 European (non-Finnish) chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs146646971) and is present in ClinVar (ID: 230926, accessed 2/22/19). In summary, the p.Lys666Asn variant meets criteria (ACMG, Richards 2015) to be classified as likely pathogenic for autosomal dominant MEN, and more specifically MTC.

Journey 1:

Test Performed
Sequence analysis and deletion/duplication testing of the 83 genes listed in the results section below.
- Invitae Multi-Cancer Panel

Reason for Testing
Family variant testing

Targeted Variants

Gene	Variant	Zygosity	Classification	Result
RET	c.1998G>T (p.Lys666Asn)	heterozygous	PATHOGENIC	Detected

Clinical Summary

- A Pathogenic variant, c.1998G>T (p.Lys666Asn), was identified in RET.
  - The RET gene is associated with autosomal dominant multiple endocrine neoplasia type 2 (MEN2) syndrome (MedGen UID: 9958) and non-syndromic Hirschsprung disease (MedGen UID: 419188).
  - This result is consistent with a predisposition to, or diagnosis of, RET-related conditions.
  - Pathogenic gain-of-function (GOF) RET variants cause MEN2, a condition associated with cancers of the endocrine glands that has three clinical subtypes: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). MEN2A is characterized by medullary thyroid carcinoma (MTC) (approximately 95%), pheochromocytoma (50% of cases) and hyperparathyroidism (approximately 20-30%). MEN2B is associated with MTC (nearly 100% of cases), pheochromocytoma (approximately 50%), while hyperparathyroidism is rare. The only clinical manifestation of FMTC is MTC (PMID: 23455356, 8918855, 19469690, 17895320). Some individuals with GOF RET variants located in exon 10 may have MEN2A and Hirschsprung disease, and therefore should have clinical evaluation for both conditions (PMID: 6136579, 10235148, 15741265, 16356097, 25810047, 19958926, 25810047).
  - Biological relatives have a chance of being at risk for RET-related conditions and should consider testing if clinically appropriate.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com or visit www.nsgc.org.

TN

"Virtual Order"

GA

11/19/2018
Test Ordered

04/29/2019
Results Received:
Multiple Endocrine Neoplasia

05/02/19
"confirmatory genetic testing, large panel due to breast lump & fam hx"

05/07/2019
Mammo/Ultrasound
05/14/2019
Breast Biopsy
Endocrine still July

05/22/2019
"Quest Direct Calcitonin"…
Results 5/25/2019

05/23/2019
"confirmatory results" received

06/07/2019
MD Anderson Endocrine

07/11/2019 &
12/16/2019
Moffitt Endocrine

Academic CGC, "aka my new best friend"…

What is the risk? Ambry, ARUP, GeneDx, Invitae, Quest, academic centers…

The impact of surveillance: Time

	Year 1	Future..
Endocrine	3 days	1-2 days
Breast	3 days	1-2 days
Skin Exams	1 day (2 @.5)	1 day (2@.5)
Total	7 days	3-5 days
Dental	1 day (2 @.5)	1 day (2 @.5)
Well Visits (PCP / GYN)	1 day (2 @.5)	1 day (2 @.5)
Vision	.5 day	.5 day
Total	2.5	2.5
	9.5	**5.5-7.5**

What about medical appointments for children or other family members? Family obligations? Childcare? Time for you?

How Much Is Average for PTO?

Ten (10) days is the average number of PTO for private sector employees who have completed one year of service, according to the Bureau of Labor Statistics (BLS).

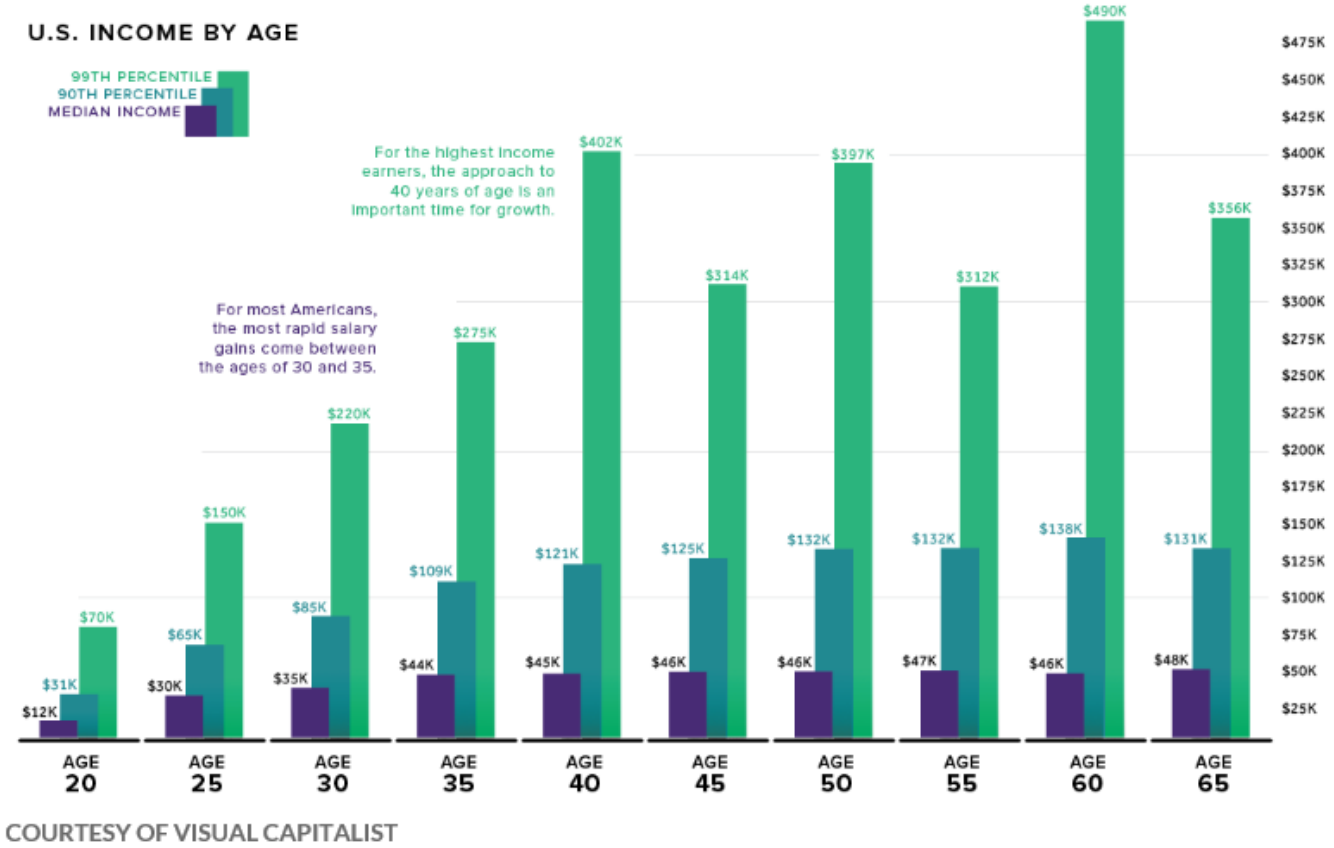
Average Number of PTO Days by Age	
18-24 years old	6.2
25-34 years old	7.8
35-44 years old	9.5
45-54 years old	**11.3**
55-64 years old	**10.4**
65+	**13.0**

https://www.zenefits.com/workest/how-much-is-average-pto-in-the-us/

The impact of surveillance: Financial

~ OOP, not including, insurance premiums: ~ $1,700 per “screen”

- Year 1 (2019): Establishing a care plan $3,354
- Current Year (2022): Continuing the care plan $2,897 & counting



This represents 6% of an annual income of 45K

Journey 2:

- Certain genetic changes in the RET gene significantly increase the risk for two different autosomal dominant hereditary conditions, multiple endocrine neoplasia type 2 (MEN2) and Hirschsprung disease.
- This is a clinically significant result that increases the risk to develop RET-related conditions.
- Individuals with MEN2 are more likely than an average person to develop multiple tumors of the endocrine system. MEN2 is divided into 3 subtypes: MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC). The most significant risk for individuals with any type of MEN2 is to develop an aggressive form of thyroid cancer known as medullary thyroid carcinoma. Features of MEN2A and MEN2B include an adrenal gland tumor known as pheochromocytoma and benign growths of the parathyroid glands, which cause hyperparathyroidism. Screening and management guidelines exist to help prevent these tumors and cancers and/or identify them at an earlier stage. It is important to recognize that this result is not a diagnosis of cancer and not all individuals with a genetic change in RET will develop cancer.
  Hirschsprung disease is an intestinal disorder characterized by the absence of nerves in parts of the intestine. This condition occurs when the nerves in the intestine do not form properly before birth. This condition is usually identified in the first two months of life, although less severe cases may be diagnosed later in childhood.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be at risk as well and could consider testing.

"Virtual Order"

2016 Preconception Genetics

"We met with a real GC and gave her all the cancer history" GC was employed by a commercial laboratory doing carrier testing

05/02/19
Attends my virtual consult for confirmatory testing

08/27/19
Genetic Counseling & Sample Collection

09/29/19
Result disclosure
Different CGC from Appt 1

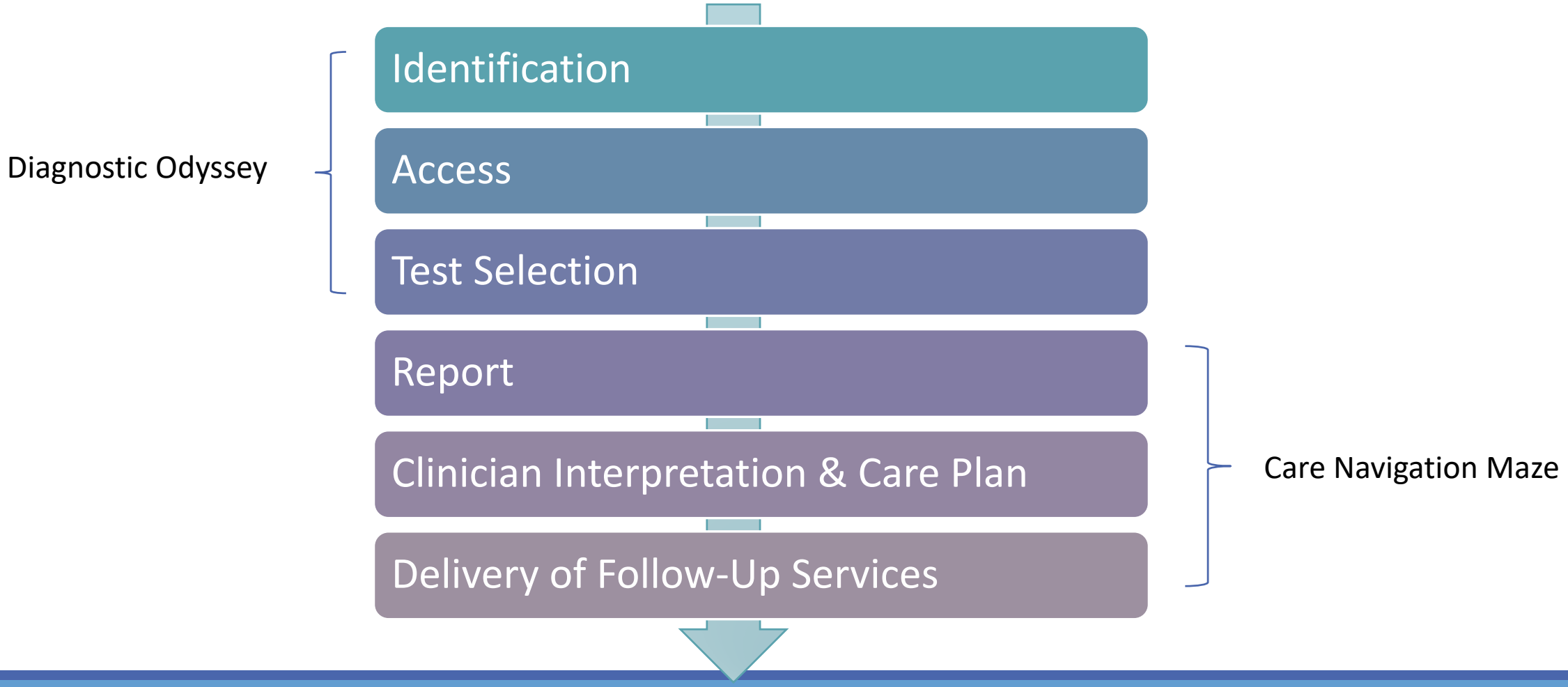
ER visit, PCP orders multiple tests, mildly elevated calcitonin, searching for a medical home

12/20/19
Moffitt CGC & Endocrine (in FL)

01/20
Surgery in GA

2020-2021
"thyroid meds"

Genetic testing process: “The report & beyond”



We must carve pathways for patients that are covered & supported by laboratories, insurers, clinicians, and employers to ensure optimal health outcomes.

Screening Impact:
>$3K a year for screening
5 annual PTO days

Surgical Impact:
Removal of normal thyroid
Medication has been challenging

"Are patients being pushed to have organ and tissue removal, instead of surveillance, due to the costs of lifetime surveillance?"*

- Preconception Consult 2016
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- 05/02/19 "confirmatory genetic testing, large panel due to breast lump & fam hx"
- 5/07/2019 Mammo/Ultrasound 05/14/2019 Breast Biopsy
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- 06/07/2019 MD Anderson Endocrine
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- 09/29/19 Result disclosure Different CGC from Appt 1
- ER visit, PCP orders multiple tests, mildly elevated calcitonin, searching for a medical home
- 12/16/2019 Moffitt Endocrine
- 12/20/19 Moffitt CGC & Endocrine
- 01/20 Surgery
- 2020-2021 "thyroid meds"

*Matloff, population genetic testing