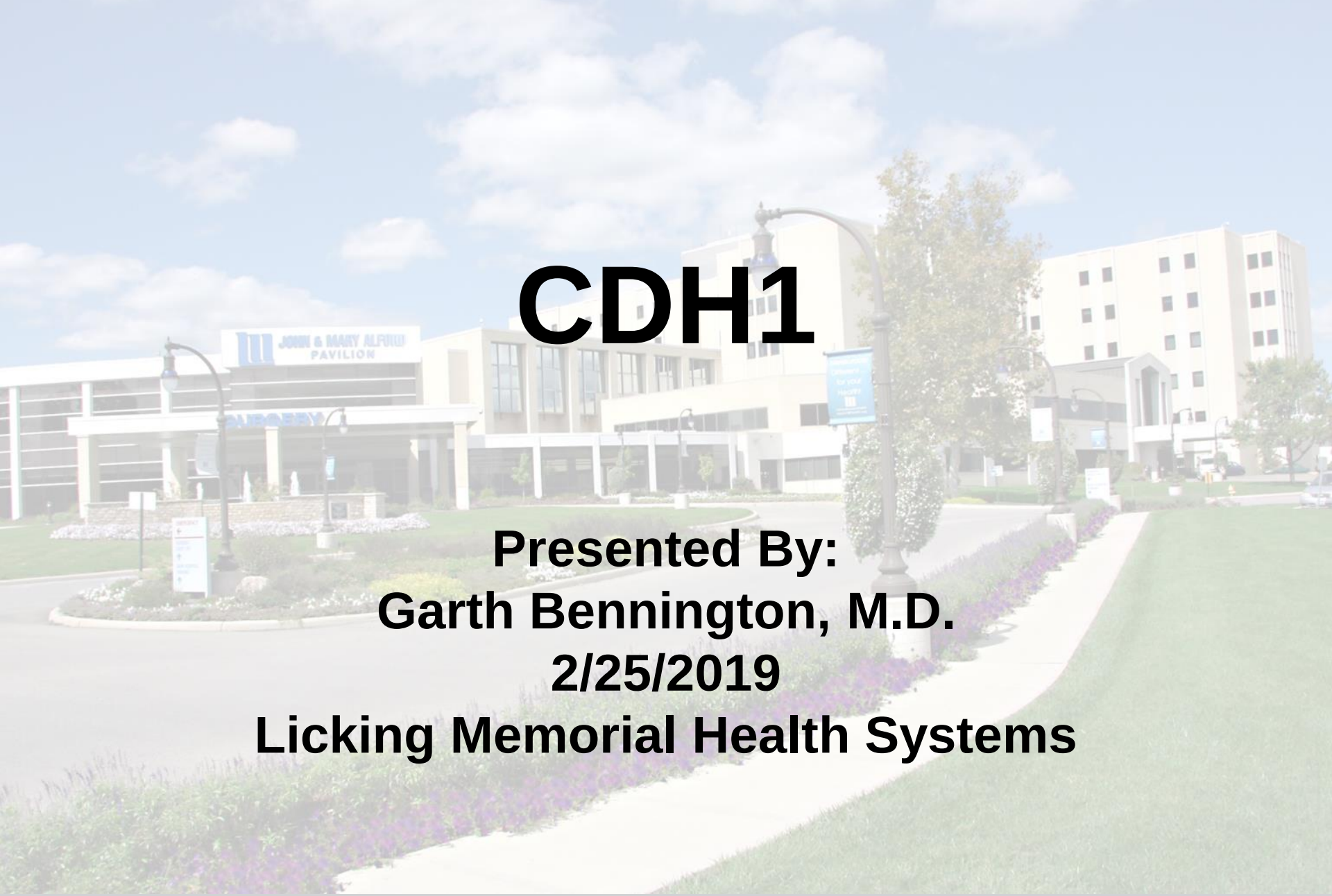


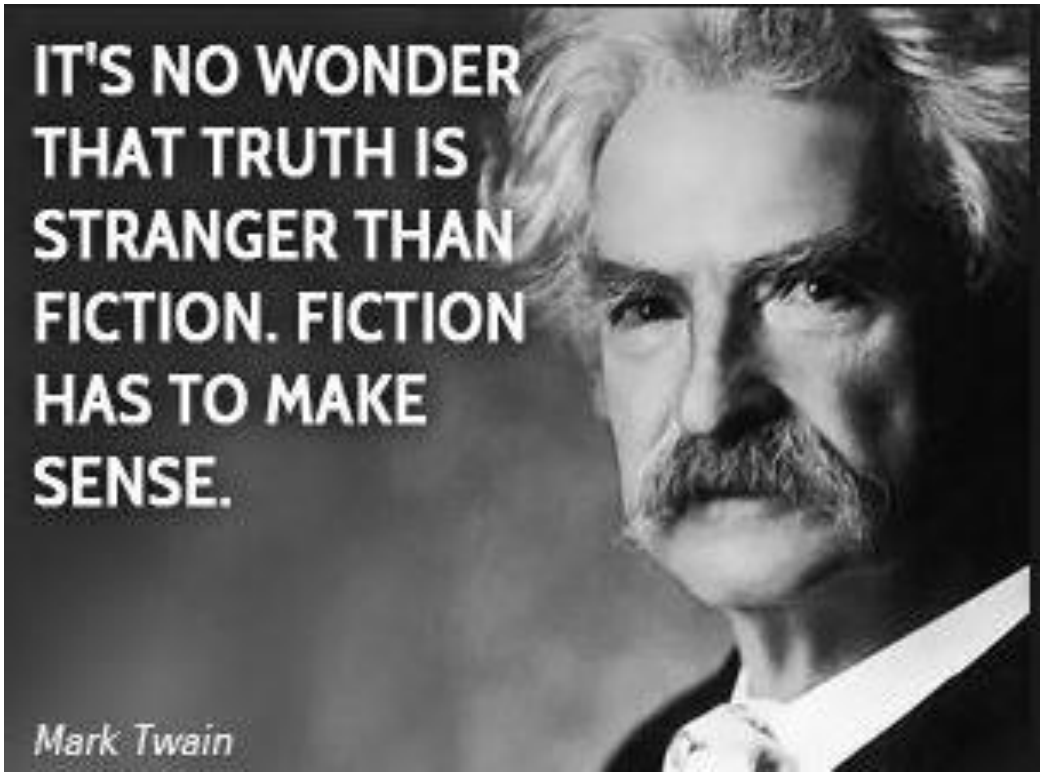
CDH1

Presented By:
Garth Bennington, M.D.
2/25/2019
Licking Memorial Health Systems

Objectives

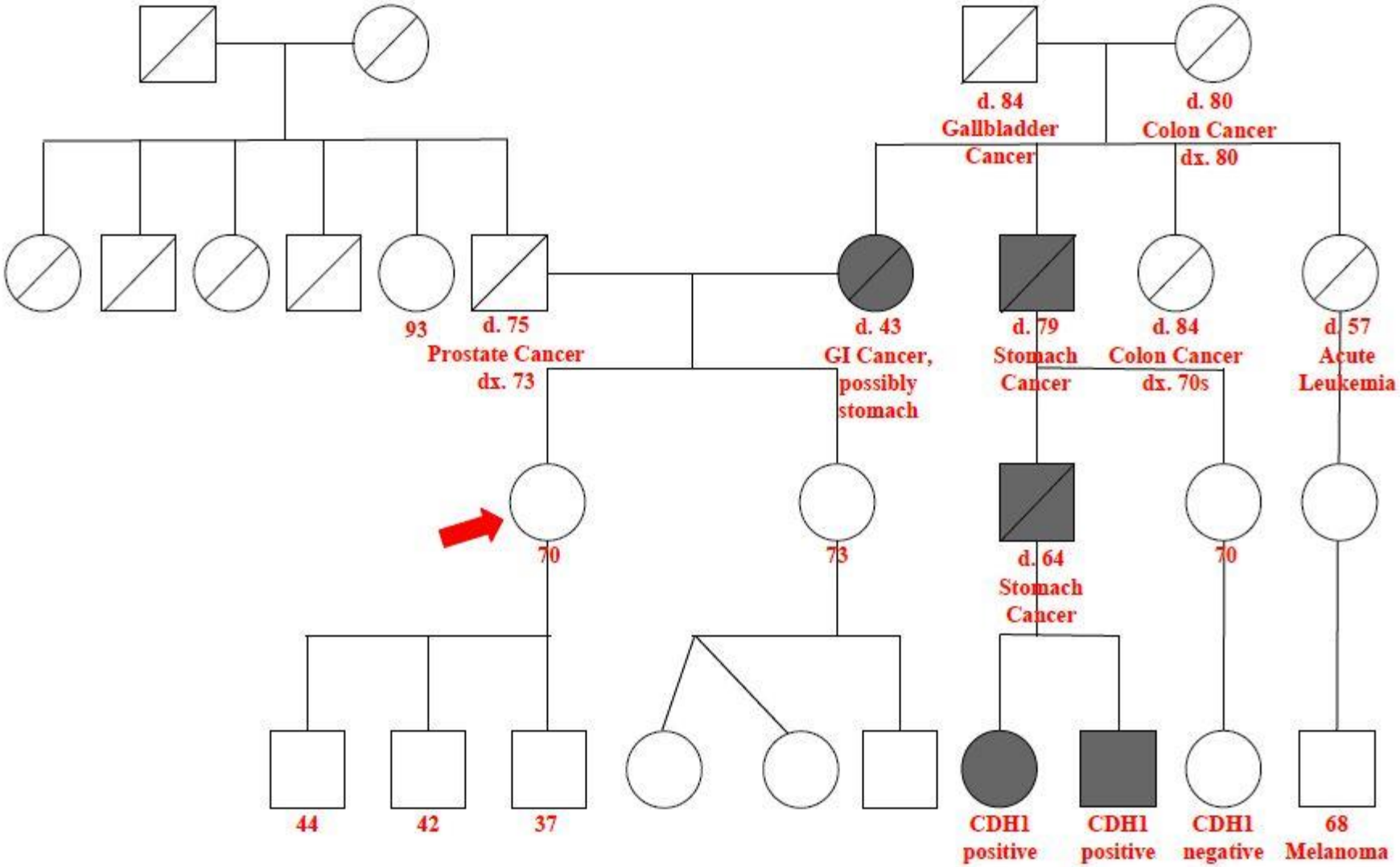
- Understand my families story of CDH1 including some practical take-away points.
- Discuss the patient population that requires testing for CDH1 and discuss how this may be applied to other autosomal dominant genetic disorders.
- Discuss the work-up and treatment for CDH1 positive patients and role of prophylactic surgery.

❖ I have no disclosures or conflicts of interest


IT'S NO WONDER THAT TRUTH IS STRANGER THAN FICTION. FICTION HAS TO MAKE SENSE.
Mark Twain

My Mothers Story

- YB is a 70 y.o. female with who presented to the OSU Genetic Counseling Clinic for evaluation by Dr. Joanne Jeter and for evaluation of any potential Genetic predispositions of cancer.
- Her only personal history of cancer was a melanoma in-situ that was treated with wide local excision. Previous screening testing for cancer including colonoscopy and mammogram had all been normal. She had no history of EGD.
- The patients most significant family history was losing her mother at age 43 to some form of GI malignancy that may have been stomach cancer. Recent discussion at a family gathering had raised concern for other family members who tested positive for gene mutation that increased their risk of developing stomach cancers. Several individuals had undergone prophylactic gastrectomy.


d. 84
Gallbladder
Cancer
d. 80
Colon Cancer
dx. 80
93
d. 75
Prostate Cancer
dx. 73
d. 43
GI Cancer,
possibly
stomach
d. 79
Stomach
Cancer
d. 84
Colon Cancer
dx. 70s
d. 57
Acute
Leukemia
70
73
d. 64
Stomach
Cancer
70
44
42
37
CDH1
positive
CDH1
positive
CDH1
negative
68
Melanoma

Genetic Testing

- Based on history and pedigree analysis my mother underwent testing for 18 genes associated with hereditary colon cancer and CDH1.

APC	Familial Adenomatous Polyposis, colon cancer
AXIN2	Elevated risk for colon cancer
BMPR1A	Juvenile Polyposis, colon cancer
CDH1	HDGC, lobular breast cancer
CHECK2	Moderate risk for breast cancer
EPCAM	Lynch syndrome-colon, uterine, ovarian, stomach, other cancers
GREM1	Elevated risk for colon cancer
MLH1	Lynch syndrome
MSH2	Lynch syndrome
MSH6	Lynch syndrome
MUTYH	MUTYH—Associated Polyposis, colon cancer
PMS2	Lynch Syndrome
POLD1	Increased risk for colorectal cancer
POLE	Increased risk for colorectal cancer
PTEN	Cowden Syndrome –breast, thyroid, uterine and non-cancer findings
SMAD4	Juvenile Polyposis, colon cancer
STK11	Peutz-Jeghers syndrome
TP53	Li-Fraumeni syndrome-breast, sarcoma, brain, adrenocortical

28 Genes Across 8 Important Cancer Types

GENES	BREAST	OVARIAN	COLORECTAL	UTERINE	MELANOMA	PANCREATIC	GASTRIC	PROSTATE	OTHER
BRCA1	●	●				●		●	
BRCA2	●	●			●	●		●	
MLH1		●	●	●		●	●	●	●
MSH2		●	●	●		●	●	●	●
MSH6		●	●	●		●	●	●	●
PMS2		●	●	●		●	●	●	●
EPCAM		●	●	●		●	●	●	●
APC			●			●	●		●
MUTYH Biallelic			●						●
MUTYH Monoallelic			●						
CDKN2A (p16INK4a)					●	●			
CDKN2A (p14ARF)					●	●			
CDK4					●	●			
TP53	●	●	●	●	●	●	●	●	●
PTEN	●		●	●	●				●
STK11	●	●	●	●		●	●		●
CDH1	●		●				●		
BMPR1A			●			●	●		●
SMAD4			●			●	●		●
PALB2	●					●			
CHEK2	●		●						
ATM	●					●			
NBN	●							●	
BARD1	●								
BRIP1		●							
RAD51C		●							
RAD51D		●							
POLD1			●						
POLE			●						
GREM1			●						

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28 Genes Across 8 Important Cancer Types

SYNDROMES	BREAST	OVARIAN	COLORECTAL	ENDOMETRIAL	MELANOMA	PANCREATIC	GASTRIC	PROSTATE	OTHER
Hereditary Breast and Ovarian Cancer syndrome (HBOC)	●	●				●		●	
Lynch syndrome/ Hereditary Non-Polyposis Colorectal Cancer (HNPCC)		●	●	●		●	●	●	●
Familial Adenomatous Polyposis (FAP)/ Attenuated Familial Adenomatous Polyposis syndrome (AFAP)			●			●	●		●
MUTYH-associated Polyposis syndrome (MAP)			●						●
MUTYH-associated Colon Cancer Risk			●						
Melanoma-Pancreatic Cancer syndrome					●	●			
Melanoma Cancer Syndrome (MCS)					●	●			
Li-Fraumeni Syndrome (LFS)	●	●	●	●	●	●	●	●	●
PTEN Hamartoma Tumor Syndrome (PHTS)	●		●	●	●				●
Peutz-Jeghers Syndrome (PJS)	●	●	●	●		●	●		●
Hereditary Diffuse Gastric Cancer (HDGC) syndrome	●		●				●		
Juvenile Polyposis Syndrome (JPS)			●			●	●		●
Juvenile Polyposis Syndrome (JPS) and Hereditary Hemorrhagic Telangiectasia (HHT)			●			●	●		●
PALB2-associated Cancer Risk	●					●			
CHEK2-associated Cancer Risk	●		●						
ATM-associated Cancer Risk	●					●			
NBN-associated Cancer Risk	●							●	
BARD1-associated Cancer Risk	●								
BRIP1-associated Cancer Risk		●							
RAD51C-associated Cancer Risk		●							
RAD51D-associated Cancer Risk		●							
Polymerase Proofreading-associated Syndrome (PPAS)			●						
Hereditary Mixed Polyposis Syndrome (HMPS)			●						

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GENETBL/1D-17

Results

- Tested was completed through Invitae.
- Pathogenic variant identified in CDH1.
  - c.1064delT (p.Leu355)
- Variant of Uncertain Significance in APC gene.

CONFIDENTIAL

52789165

Single Site Analysis

myRisk Genetic Result

MYRIAD myRisk® Hereditary Cancer | Powered by myVision®

RECEIVING HEALTHCARE PROVIDER

[redacted]

Newark, OH 43055

SPECIMEN

Specimen Type: Blood
Draw Date: Jul 05, 2017
Accession Date: Jul 06, 2017
Report Date: Jul 19, 2017

PATIENT

Name: [redacted]
Date of Birth:
Patient ID:
Gender: Male
Accession #: 02645510-BLD
Requisition #: 5637968

ORDERING PHYSICIAN: Lori Elwood, MD

RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

TEST PERFORMED	RESULT	INTERPRETATION
CDH1	**Mutation Detected**	**High Cancer Risk**
c.1064del (p.Leu355*)	Heterozygous	This patient has Hereditary Diffuse Gastric Cancer (HDGC) Syndrome.

DETAILS ABOUT: *CDH1* c.1064del (p.Leu355*): NM_004360.3

Functional Significance: Deleterious - Abnormal Protein Production and/or Function

The heterozygous germline *CDH1* mutation c.1064del is predicted to result in the premature truncation of the *CDH1* protein at amino acid position 355 (p.Leu355*).

Clinical Significance: High Cancer Risk

This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

ADDITIONAL INFORMATION

GENES ANALYZED

Analysis was performed on the mutation(s) specified above.

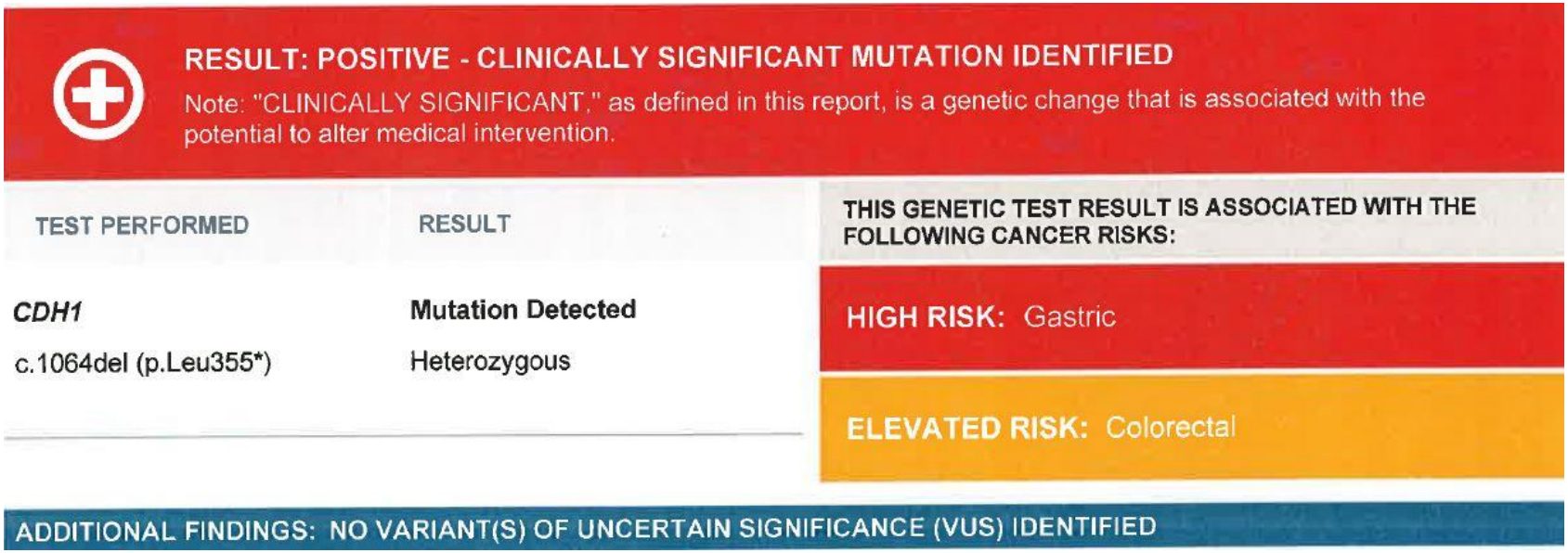
The following comment applies only if this patient was tested for a variant that was originally detected in a laboratory other than Myriad. Laboratories sometimes differ in the way they name genetic variants, and there are also cases where the ability to detect a variant could differ based on testing technology. Rare instances can occur where these differences result in a patient receiving an incorrect result. Any concerns about this possibility can be addressed by submitting a specimen to Myriad from the relative in whom the variant was originally detected. If you would like to discuss this option, please contact Myriad Medical Services at 1-800-469-7423 X 3850.

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Please see the "myRisk Management Tool" associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications/) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. The interpretation of this test may be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant.

Genetic Testing



RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

TEST PERFORMED	RESULT
CDH1	**Mutation Detected**
c.1064del (p.Leu355*)	Heterozygous

THIS GENETIC TEST RESULT IS ASSOCIATED WITH THE FOLLOWING CANCER RISKS:

HIGH RISK: Gastric

ELEVATED RISK: Colorectal

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

- Clincally significant mutation detected
- Heterozygous Pathogenic Variant identified in CDH1.

Genetic Testing

OVERVIEW

Hereditary Diffuse Gastric Cancer (HDGC) Syndrome:

- This patient has been found to have a mutation in the *CDH1* gene. Individuals with mutations in *CDH1* have a condition called Hereditary Diffuse Gastric Cancer syndrome (HDGC).
- Patients with HDGC have a high risk for the diffuse form of gastric cancer, which is less common than intestinal type gastric cancer. Diffuse gastric cancer is more difficult to detect with endoscopic screening because it typically forms without a distinct mass. The majority of gastric cancers in individuals with HDGC are diagnosed under age 40, with some diagnoses occurring in the mid-teens.
- Women with HDGC have a risk for lobular breast cancer that is significantly increased over the 12.5% lifetime breast cancer risk for women in the general population of the United States. The risk for male breast cancer is not thought to be increased.
- It is currently not certain that patients with HDGC have an increased risk for colorectal cancer, but there is enough suspicion of an increased risk to recommend special screening.
- Guidelines for the medical management of patients with HDGC have been developed by the International Gastric Cancer Linkage Consortium (IGCLC) and the National Comprehensive Cancer Network (NCCN). These are listed below. It is recommended that patients with *CDH1* mutations and a diagnosis of HDGC be managed by a multidisciplinary team with expertise in medical genetics, gastric surgery, gastroenterology, pathology and nutrition.

WHAT ARE THE PATIENT'S GENE-RELATED CANCER RISKS?

If more than one gene mutation increases a specific cancer risk (e.g., breast), only the highest cancer risk is shown. If this patient has more than one gene mutation, risks may be different, as this analysis does not account for possible interactions between gene mutations.

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION	RELATED TO
GASTRIC			
To age 80	67%-70%	0.6%	*CDH1*
COLORECTAL			
To age 80	Possibly elevated risk	3.4%	*CDH1*

WHAT MANAGEMENT FOR CANCER RISKS SHOULD BE CONSIDERED?

This overview of clinical management guidelines is based on this patient's genetic test results. Unless otherwise stated, medical management guidelines are limited to those issued by the National Comprehensive Cancer Network (NCCN). The reference provided should always be consulted for more details. If management for a specific cancer (e.g. breast) is available due to multiple mutations, only the most aggressive management is shown. Only guidelines for the patient's long-term care related to cancer prevention are included.

No information is provided related to treatment of a previous or existing cancer or polyps. These recommendations may require modification based on the patient's personal medical history, surgeries and other treatments. Patients with a personal history of cancer, benign tumors or pre-cancerous findings may be candidates for long term surveillance and risk-reduction strategies beyond what is necessary for the treatment of their initial diagnosis. Any discussion of medical management options is for general information purposes only and does not constitute a recommendation. While genetic testing and medical society guidelines provide important and useful information, medical management decisions should be made in consultation between each patient and his or her healthcare provider.

Genetic Testing

PROCEDURE	AGE TO BEGIN	FREQUENCY (Unless otherwise indicated by findings)	RELATED TO
GASTRIC			
Gastrectomy[2]	18 to 40 years, or individualized to a younger age if a relative was diagnosed under age 25	NA	*CDH1*
Baseline endoscopy prior to gastrectomy. Endoscopies with targeted biopsies may be appropriate for patients delaying or declining gastrectomy.[1,2]	Individualized	Every 6 to 12 months	*CDH1*
Treat for Helicobacter pylori infection if present.[1]	Individualized	NA	*CDH1*
COLORECTAL			
Consider colonoscopy for patients with a family history of colorectal cancer.[1]	Individualized	Individualized	*CDH1*

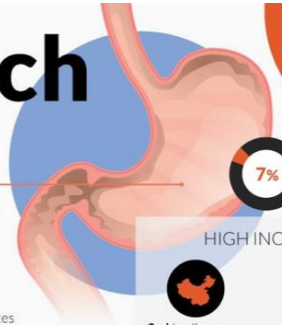
Genetic Testing

- This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.
- **Family members should talk to a healthcare provider about genetic testing.** Close relatives such as parents, children, brothers, and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance for carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention. More resources for family testing are available at MySupport360.com.
- There is an increased risk for children who inherit a *CDH1* mutation to be born with a cleft lip and/or palate. This risk may be higher in families in which clefts have occurred previously.

CANCER RISK FOR *CDH1* CLINICALLY SIGNIFICANT MUTATION

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION
FOR FEMALE RELATIVES		
GASTRIC		
To age 80	56%-83%	0.6%
FEMALE BREAST		
To age 50	10%	1.9%
To age 80	39%-52%	10.2%
FOR MALE RELATIVES		
GASTRIC		
To age 80	67%-70%	0.6%
FOR FEMALE AND MALE RELATIVES		
COLORECTAL		
To age 80	Possibly elevated risk	3.4%

Stomach Cancer



Over **1,000,000** Number of new Stomach Cancer cases globally in 2018 [1]

7% Of new cancer cases globally each year that are stomach malignancies [1]

DEFEATING ONE OF THE WORLD'S MOST THREATENING DISEASES

Stomach Cancer affects a population nearly the size of Hawaii. With close to a million new cases occurring globally each year, it's the 5th most common cancer in the world. [1] Although global incidence and mortality rates continue to decline, these vary drastically between countries due to wide discrepancies in exposure to risk factors and standard treatment and prevention.

HIGH INCIDENCE COUNTRIES

2nd leading cause of cancer death in China [2]

Most common fatal malignancy in Japan until 1995 [3]

The Republic of Korea had the highest rate of stomach cancer for both men and women in 2012 [4]

RISK FACTORS

In some cases, Stomach Cancer results from a genetic mutation of the **CDH1 gene**. This is disproportionately common for native New Zealanders (Maori).

1-3% Of cases known to be caused by genetic mutations [5]

3X Higher risk of Stomach Cancer experience **by Maori Population** [6]

However, researchers suggest most cases of Stomach Cancer occur due to factors like:

- **H. pylori Infection**
- **Smoking**
- **Chemical exposure**
- **Salt preservatives**
- **Excessive alcohol**
- **Obesity**
- **Low fruit and vegetable intake**

11% Of worldwide cases **attributed to tobacco** [7]

GLOBAL PERSPECTIVE

1 in 111 people are at risk of Stomach Cancer worldwide, [8] with the majority of Stomach Cancer cases occuring outside the U.S.

1/2 Number of world cases occurring in **East Asia** (mainly in China) [1]

70% Of cases in **developing countries** [1]

TREATMENT

For many patients, treatment requires stomach removal. Symptoms often appear only in later stages of the disease, leading to lower recovery rates and a need for more intense treatment. For example, in Germany, only **10% to 20% of cases are diagnosed in early stages.** [9]

28.5% Five-year relative survival rate of Stomach Cancer Patients in Australia [10]

In South Korea 5 year survival levels are high at **68.9%** [11]

HOPE FOR THE FUTURE

Fortunately, Stomach Cancer rates are declining worldwide. In the UK, this cancer in particular has shown the fastest decrease in mortality over the past decade [12]

Decline is largely thanks to:

Fewer H. pylori infections

Reduced need for salt preservatives

Better measures for detection and preven-

MAKE AN IMPACT Share this infographic and contribute to the fight against Stomach Cancer and help support thousands, who are shedding light on this disease.

Visit **www.nostomachforcancer.org** to learn more

SOURCES

1. globocan.iarc.fr
2. ncbi.nlm.nih.gov
3. jstage.jst.go.jp
4. wcrf.org
5. tgh.amegroups.com
6. hopkinsmedicine.org
7. otago.ac.nz
8. No Stomach For Cancer
9. aicr.org
10. aihw.gov.au
11. csg.lshtm.ac.uk
12. cancerresearchuk.org

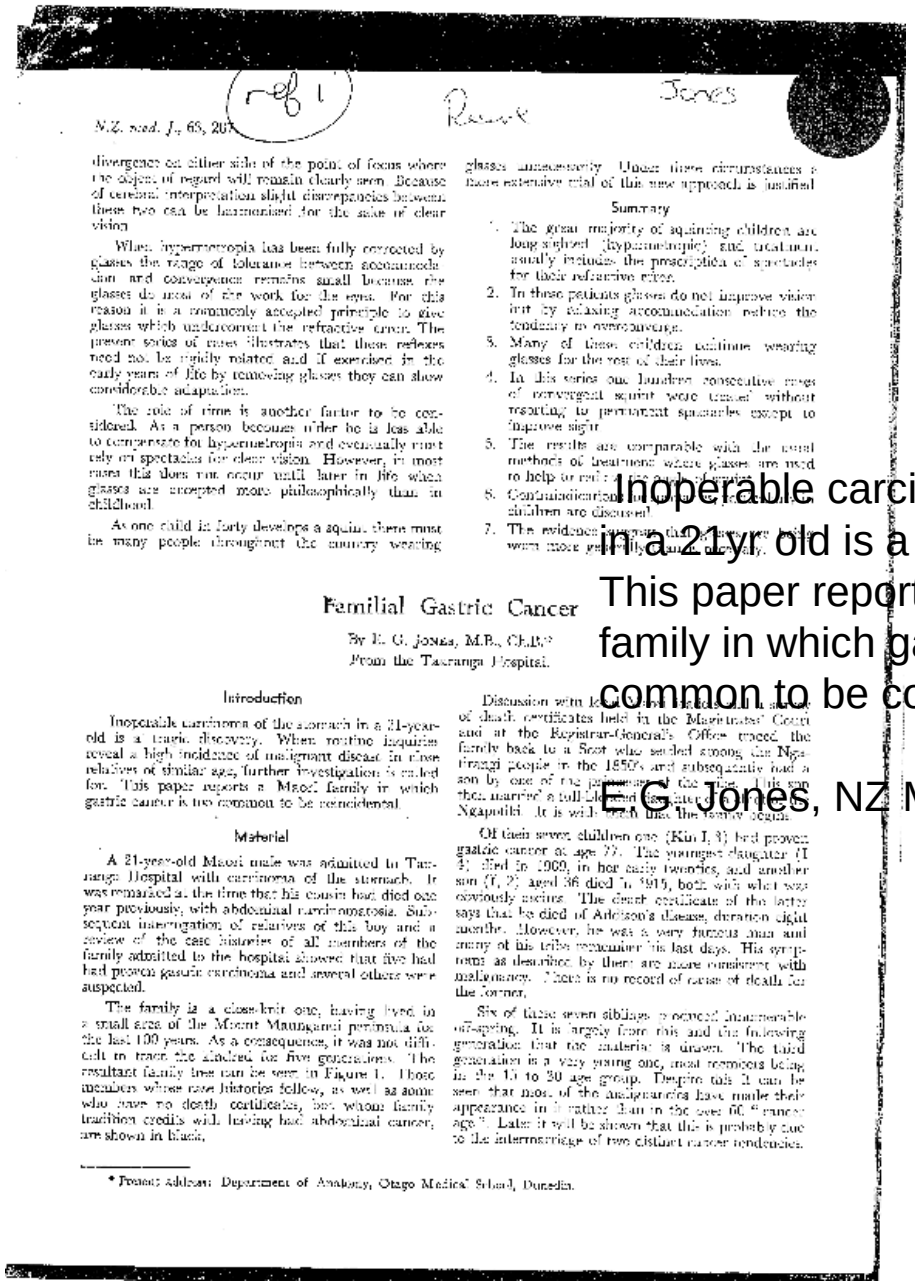
Gastric Cancer

- 5th most common cancer worldwide
- Approximately 22,220 patients are diagnosed annually in the US.
- Much more common in Eastern Asia, Eastern Europe, and South America.
- Worldwide incidence declining rapidly over the past few decades. - ? H. pylori, salt preservation.

CDH1-Hereditary Diffuse Gastric Cancer (HDGC)

- Vast major of gastric cancer is sporadic.
- 1-3% of gastric cancer arises from inherited cancer predisposition syndromes.
- Other syndromes that can cause gastric cancer to lesser degree is Li-Fraumeni syndrome, Lynch syndrome, Peutz-Jeghers syndrome, Hereditary breast and ovarian cancer, MAP, FAP, Juvenile polyposis syndrome, PTEN hamartoma tumor syndrome.
- HDGC is an inherited form of diffuse-type of gastric cancer.
- It tends to be a highly invasive tumor that is characterized by late presentation and a poor prognosis.
- Lifetime risk of gastric cancer and lobular breast cancer are high.
- Median age of gastric cancer is 38.

1964



ref 1 Jones

N.Z. med. J., 63, 20?

divergence on either side of the point of focus where the object of regard will remain clearly seen. Because of cerebral interpretation slight discrepancies between these two can be harmonised for the sake of clear vision.

When hypermetropia has been fully corrected by glasses the range of tolerance between accommodation and convergence remains small because the glasses do most of the work for the eyes. For this reason it is a commonly accepted principle to give glasses which undercorrect the refractive error. The present series of cases illustrates that these reflexes need not be rigidly related and if exercised in the early years of life by removing glasses they can show considerable adaptation.

The role of time is another factor to be considered. As a person becomes older he is less able to compensate for hypermetropia and eventually must rely on spectacles for clear vision. However, in most cases this does not occur until later in life when glasses are accepted more philosophically than in childhood.

As one child in forty develops a squint there must be many people throughout the country wearing glasses unnecessarily. Under these circumstances a more extensive trial of this new approach is justified.

Summary

1. The great majority of squinting children are long-sighted (hypermetropic) and treatment usually includes the prescription of spectacles for their refractive error.
2. In these patients glasses do not improve vision but by relaxing accommodation reduce the tendency to overconverge.
3. Many of these children continue wearing glasses for the rest of their lives.
4. In this series one hundred consecutive cases of convergent squint were treated without resorting to permanent spectacles except to improve sight.
5. The results are comparable with the usual methods of treatment where glasses are used to help to relieve [illegible]
6. Contraindications [illegible] children are discussed.
7. The evidence [illegible] were more [illegible]

Familial Gastric Cancer

By E. G. Jones, M.B., Ch.B.*
From the Tauranga Hospital.

Introduction

Inoperable carcinoma of the stomach in a 21-year-old is a tragic discovery. When routine inquiries reveal a high incidence of malignant disease in close relatives of similar age, further investigation is called for. This paper reports a Maori family in which gastric cancer is too common to be coincidental.

Material

A 21-year-old Maori male was admitted to Tauranga Hospital with carcinoma of the stomach. It was remarked at the time that his cousin had died one year previously, with abdominal carcinomatosis. Subsequent interrogation of relatives of this boy and a review of the case histories of all members of the family admitted to the hospital showed that five had had proven gastric carcinoma and several others were suspected.

The family is a close-knit one, having lived in a small area of the Mount Maunganui peninsula for the last 100 years. As a consequence, it was not difficult to trace the kindred for five generations. The resultant family tree can be seen in Figure 1. Those members whose case histories follow, as well as some who have no death certificates, but whom family tradition credits with having had abdominal cancer, are shown in black.

Discussion with [illegible] of death certificates held in the Magistrates' Court and at the Registrar-General's Office traced the family back to a Scot who settled among the Ngatiranga people in the 1850's and subsequently had a son by one of the [illegible] daughters. This son then married a full-[illegible] Ngapoliki. It is with [illegible]

Of their seven children one (Kin I, 3) had proven gastric cancer at age 77. The youngest daughter (I 4) died in 1909, in her early twenties, and another son (I, 2) aged 36 died in 1915, both with what was obviously ascites. The death certificate of the latter says that he died of Addison's disease, duration eight months. However, he was a very famous man and many of his tribe remember his last days. His symptoms as described by them are more consistent with malignancy. There is no record of cause of death for the former.

Six of these seven siblings [illegible] offspring. It is largely from this and the following generation that the material is drawn. The third generation is a very young one, most members being in the 15 to 30 age group. Despite this it can be seen that most of the malignancies have made their appearance in a rather than in the over 60 "cancer age". Later it will be shown that this is probably due to the intermarriage of two distinct cancer tendencies.

* Present Address: Department of Anatomy, Otago Medical School, Dunedin.

Inoperable carcinoma of the stomach in a 21yr old is a tragic discovery…. This paper reports a Maori family in which gastric cancer is too common to be coincidental."

E G Jones, NZ Medical Journal, 1964.

Parry Guilford

Identification of CDH1 in Hereditary Diffuse Gastric Cancer

- Maori people felt they were cursed for selling their burial land for quarrying purposes.
- In 1994, family member Maybelle McLeod got funding from the Health Research Council to employ a scientist to search for answers.
- Based on Linkage and mutational analysis, Dr. Guilford identified germline mutations affecting the gene coding for the cell-cell adhesion molecule E-cadherin (CDH1) in large multi-generational New Zealand Maori Family.
- In 2015 approximately 500 families worldwide.

MENU

nature
International journal of science

Letter | Published: 26 March 1998

E-cadherin germline mutations in familial gastric cancer

Parry Guilford ✉, Justin Hopkins, James Harraway, Maybelle McLeod, Ngahiraka McLeod, Pauline Harawira, Huriana Taite, Robin Scoular, Andrew Miller & Anthony E. Reeve

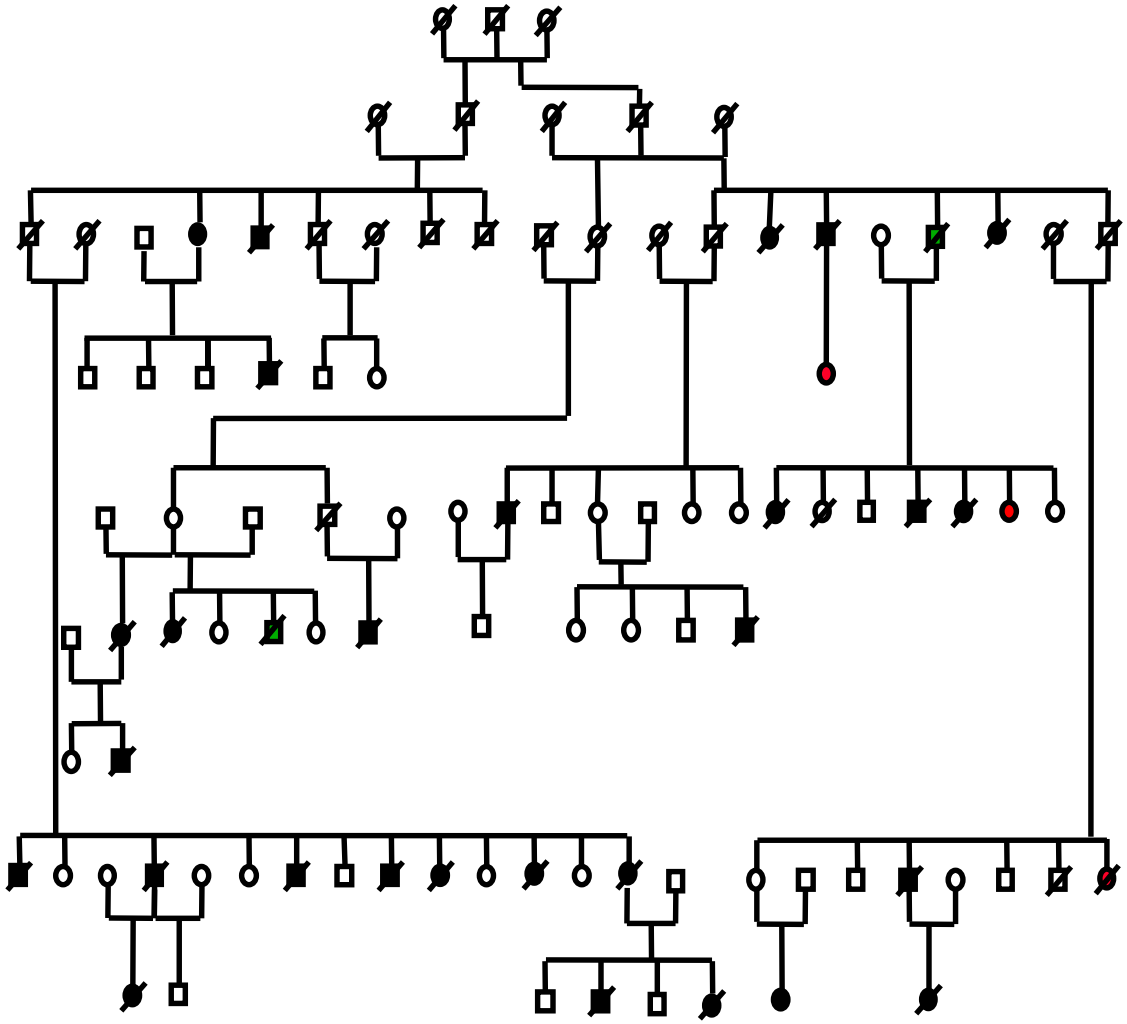
Nature **392**, 402–405 (26 March 1998) | Download Citation ⬇

Hereditary diffuse gastric cancer (HDGC)

- Dominant inheritance of germline *CDH1* mutation

- Diffuse gastric cancer *70% lifetime risk*
- Lobular breast cancer *~40% risk*

>500 known families worldwide



Family A

Identification of CDH1 in Hereditary Diffuse Gastric Cancer/Lobular Breast Cancer

- E-cahedrin is a tumor suppressor protein.
- Pathogenic variants of the CDH1 gene were located on chromosome 16q22.1.
- To date over 155 different mutations have been identified. Most mutations are pathogenic but some variants of uncertain significance have also been identified.
- HDGC is inherited in autosomal dominant manner with high penetrance
- Lifetime cumulative risk for advanced diffuse-type gastric cancer is around 70% for males and 56% for females.
- Average age of onset is 38 but has been reported from age 14-82 years.
- Lifetime risk for lobular breast cancer is 42%.
- CDH1 is tumor suppressor gene therefore felt that a second hit is required for intiation of tumor formation.

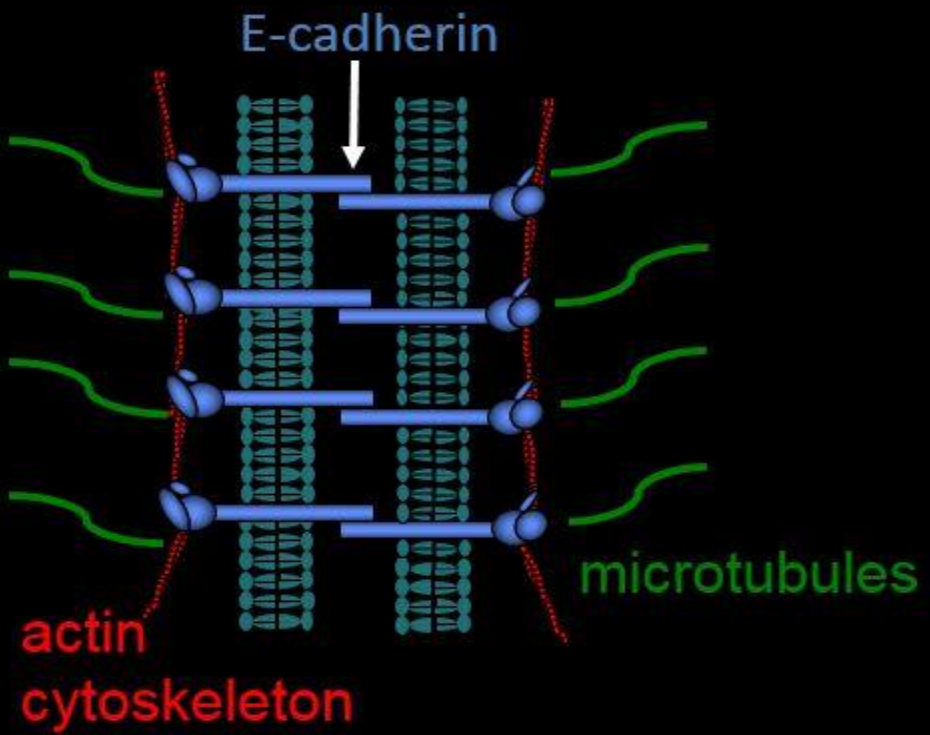
E-cadherin *(CDH1)*

- Cell-cell adhesion protein
  - *Tissue integrity*
  - *Cell polarity*
  - *Differentiation*
  - *Survival signaling*

- Tumour suppressor gene

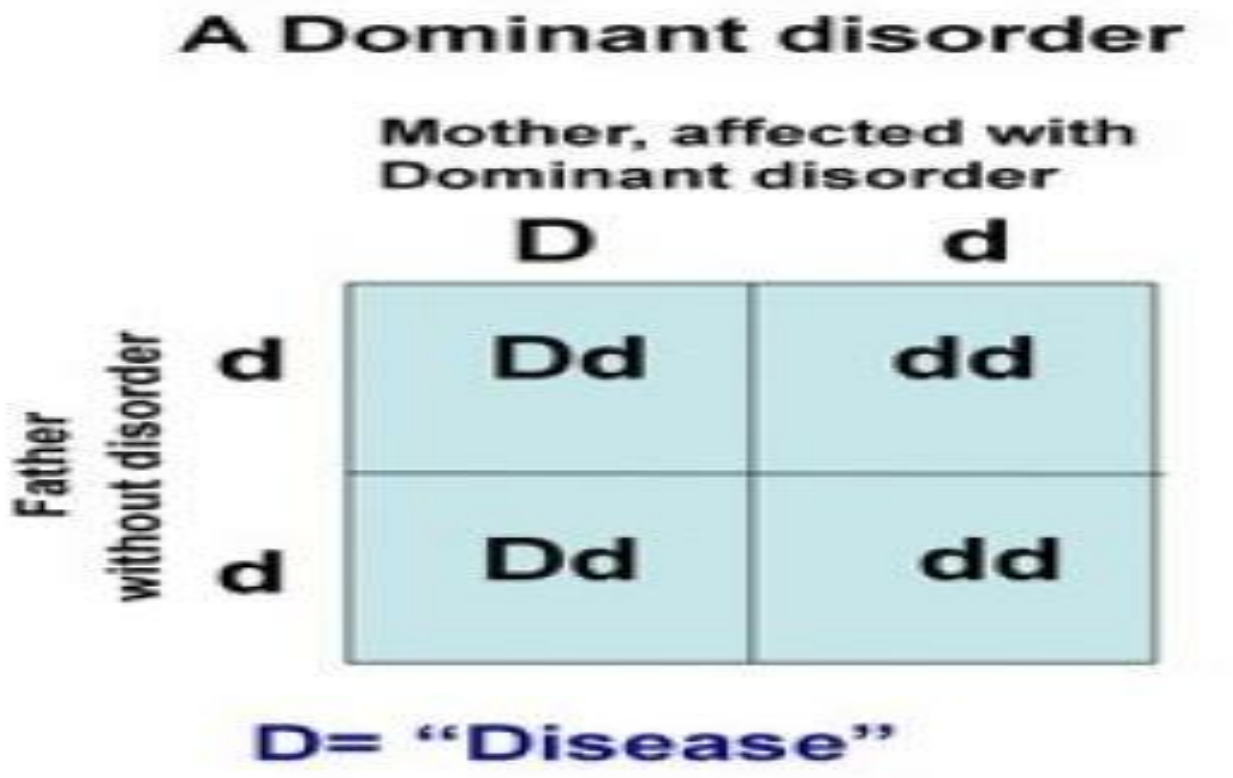
Somatic mutations in diffuse-type stomach cancer (DGC) and lobular breast cancer (LBC)

Germline mutations cause hereditary diffuse gastric cancer



Need for chemoprevention and treatment of these cancers

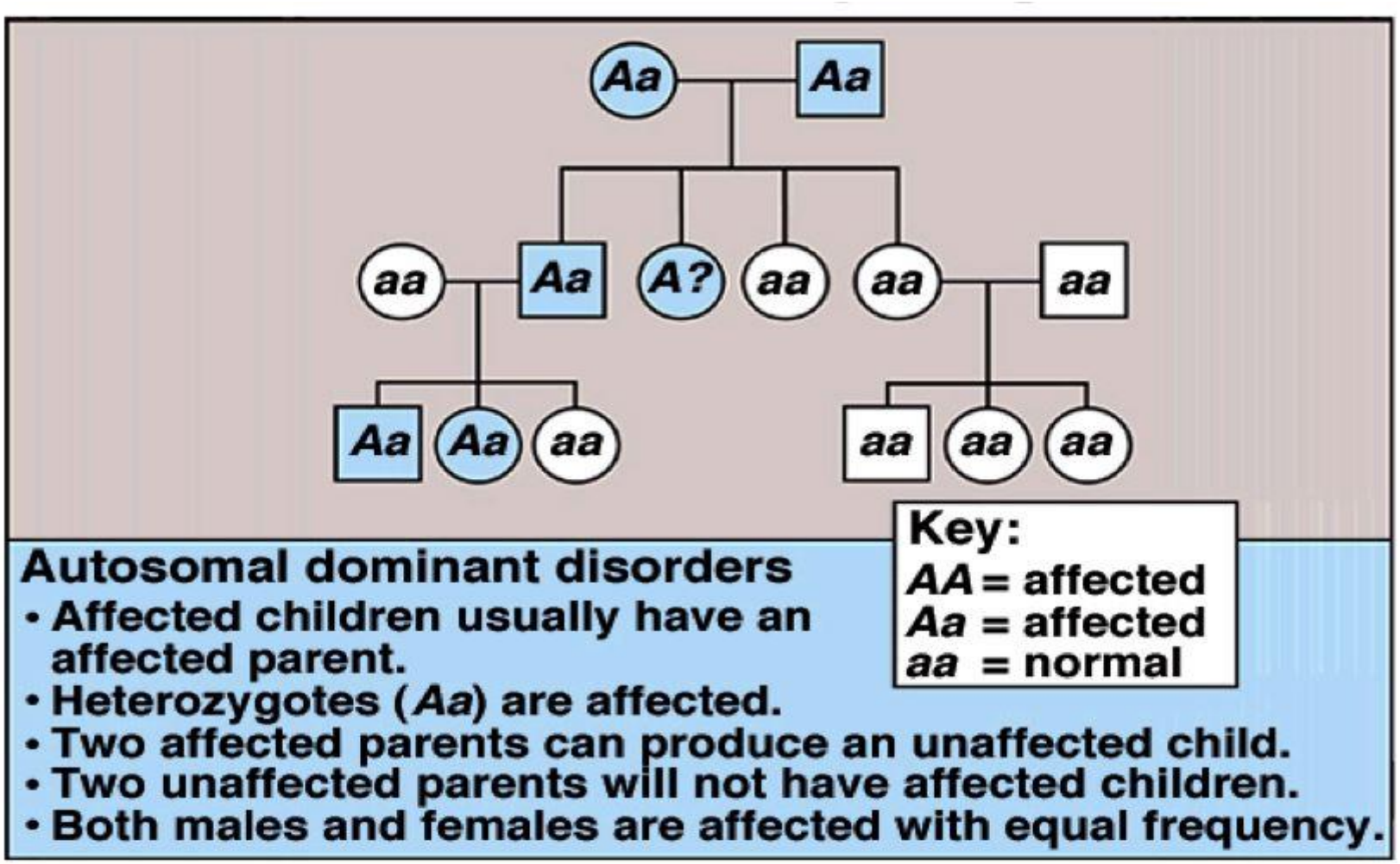
2 Hit Hypothesis and Autosomal Disorder

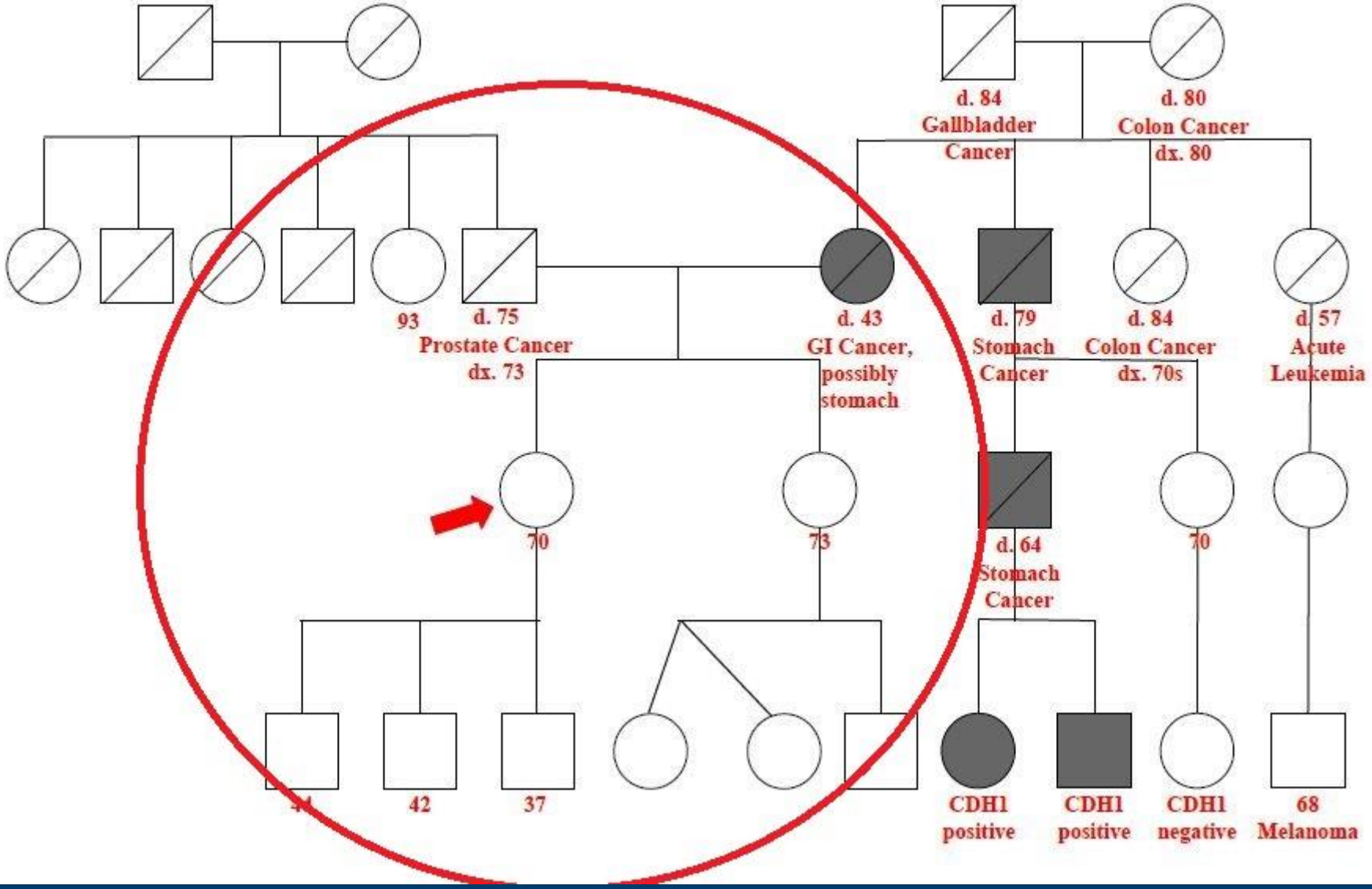


2 Hit Hypothesis and Autosomal Disorder

- Knudson suggested that multiple "hits" to DNA were necessary to cause cancer.
- In the children with inherited retinoblastoma, the first mutation was inherited in the DNA, and any second mutation would rapidly lead to cancer.
- In non-inherited retinoblastoma, two "hits" had to take place before a tumor could develop, explaining the age difference.
- A mutation in both alleles is required, as a single functional tumor suppressor gene is usually sufficient for a normal functioning protein.

2 Hit Hypothesis and Autosomal Disorder




d. 84
Gallbladder
Cancer
d. 80
Colon Cancer
dx. 80
93
d. 75
Prostate Cancer
dx. 73
d. 43
GI Cancer,
possibly
stomach
d. 79
Stomach
Cancer
d. 84
Colon Cancer
dx. 70s
d. 57
Acute
Leukemia
70
73
d. 64
Stomach
Cancer
70
44
42
37
CDH1
positive
CDH1
positive
CDH1
negative
68
Melanoma

Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline *CDH1* mutation carriers

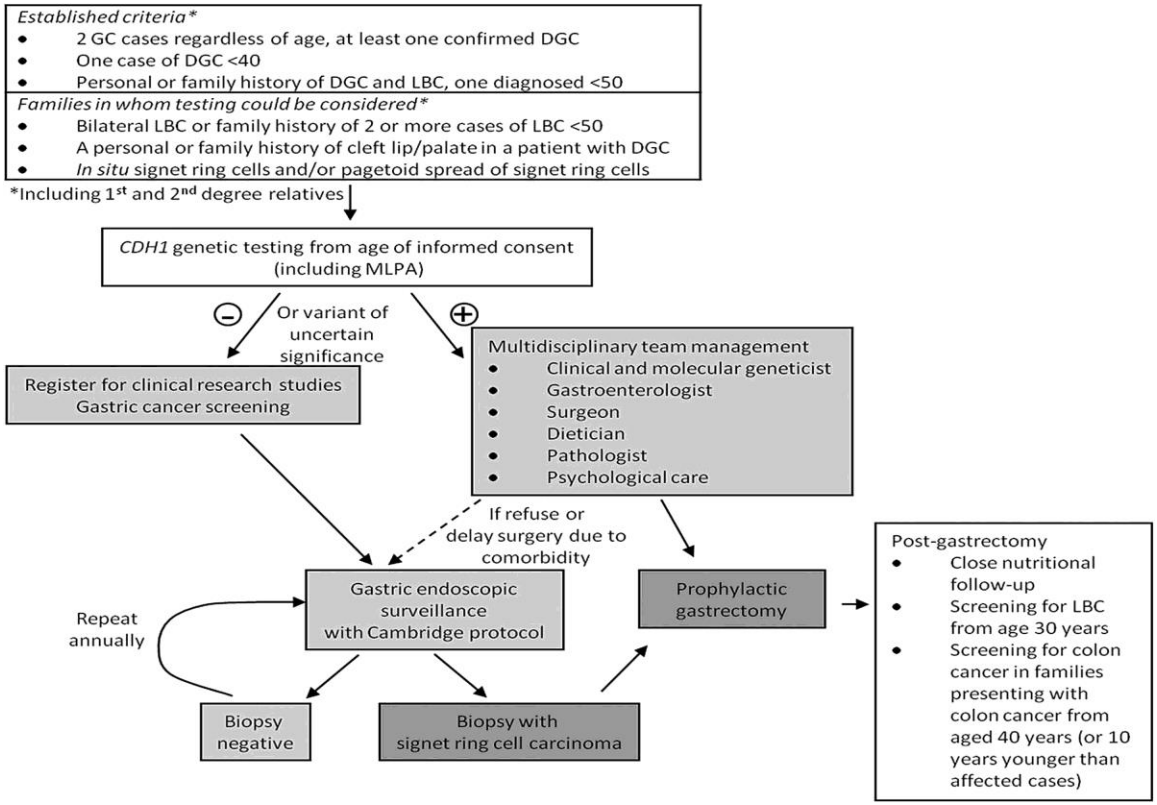


Figure 1. Algorithm for management starting from clinical hereditary diffuse gastric cancer (HDGC) testing criteria, genetic testing, role of endoscopy and gastrectomy. GC, gastric cancer; DGC, diffuse gastric cancer; LBC, lobular breast cancer; MLPA, multiplex-ligation probe amplification.

Who Should be Tested

- Criteria for testing
  - 2 gastric cancer cases regardless of age, at least one confirmed diffuse gastric cancer
  - one case DGC<40
  - Personal or family history of DGC and LBC, one diagnosed <50
  - These include 1st and 2nd degree relatives
- Consider testing
  - Bilateral LBC or family history of 2 or more cases of LBC <50
  - A personal family history of cleft lip/palate in a patient with DGC
  - In situ signet ring cells and/or pagetoid spread of signet ring cells (rarely seen in sporadic cases)

Multidisciplinary Team Management

- Clinical and molecular geneticist
- Gastroenterologist
- Surgeon
- Pathologist
- Psychological care

Back to the Story…

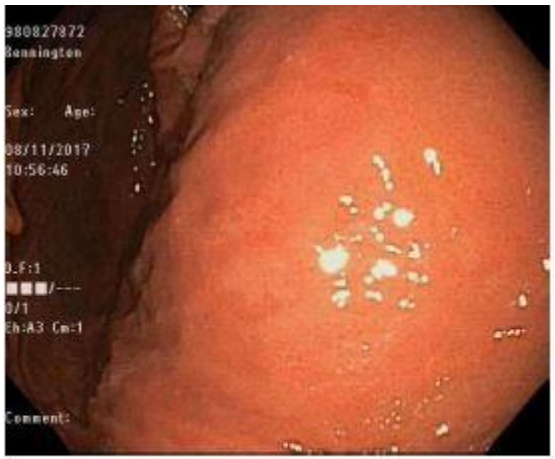
- Following my mother's positive CDH1 testing I underwent testing and July 18th was found to be positive as well
- My brother then tested positive for CDH1
- So now what..

Protocol for endoscopy

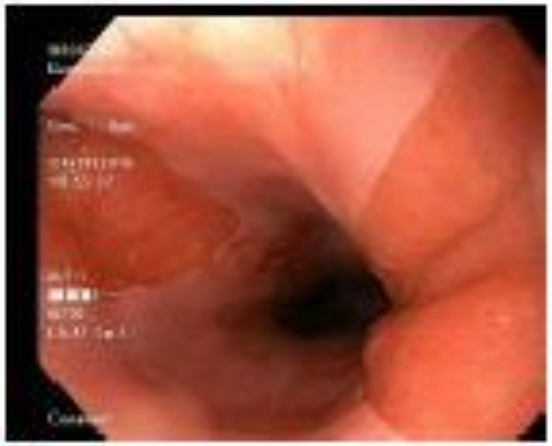
- Use white light high definition scope.
- Endoscopy to be performed using high definition zoom gastroscope and use of mucolytics such as N-acetylcysteine is encouraged to obtain good visualization
- Stomach should be inflated and deflated to rule out submucosal infiltrate like *linitis plastica*.
- Biopsies should be taken of any endoscopically visable lesions – specifically looking for pale lesions
- Random sampling should be performed comprising five biopsies taken from each of the following anatomical zones: pre-pyloric area, antrum, transitional zone, body, fundus and cardia
- A minimum of 30 biopsies is recommended as described in the Cambridge protocol
- Test for h. pylori.

Back to the story…

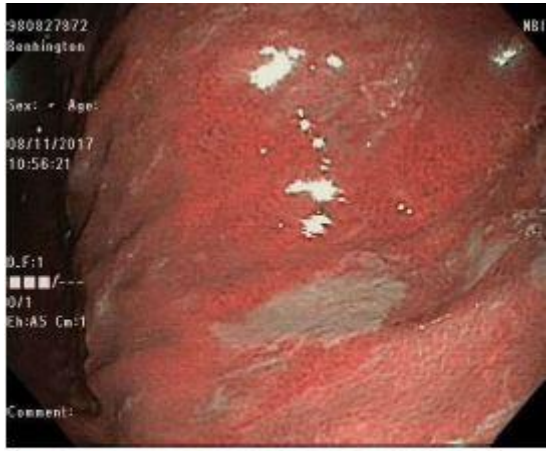
- Both my Mother and I undergo endoscopy with Dr. Peter Stanich at The Ohio State University.



22 Lesser Curvature : Abnormal Mucosa



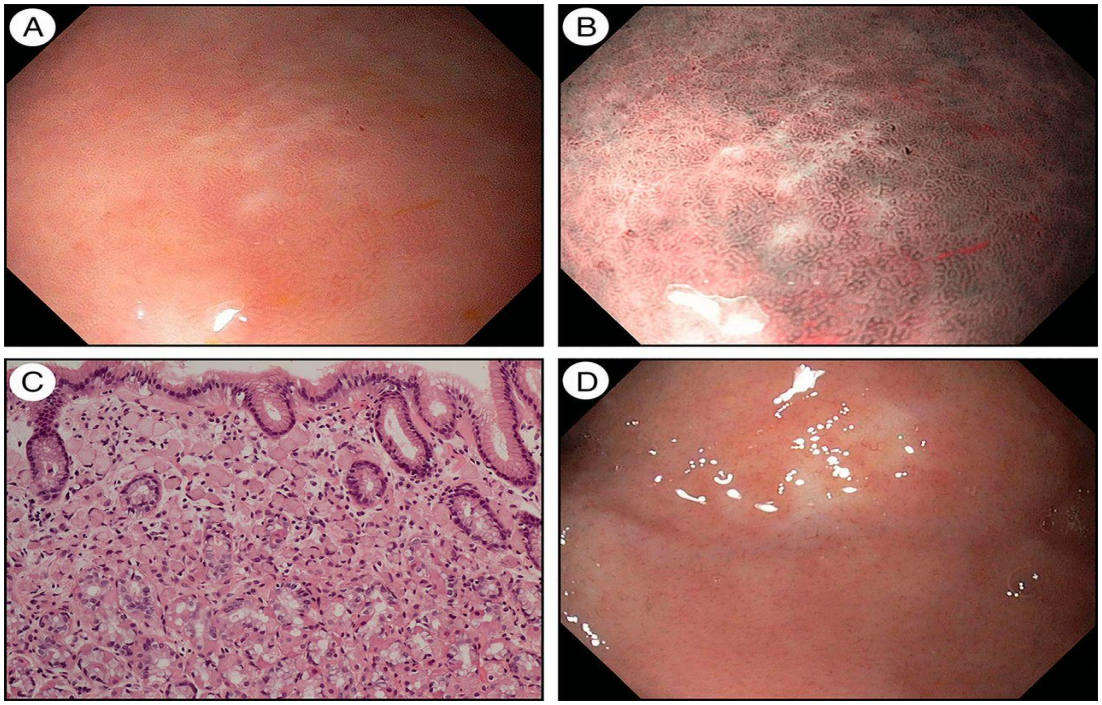
1 Upper Third of the Esophagus : Ectopic gastric mucosa



19 Lesser Curvature : Abnormal Mucosa

Signet Ring Cells

Pale areas in gastric mucosa of a patient with a germline CDH1 mutation harbouring signet ring cell focus during white light endoscopy (A) and narrow band imaging (B).



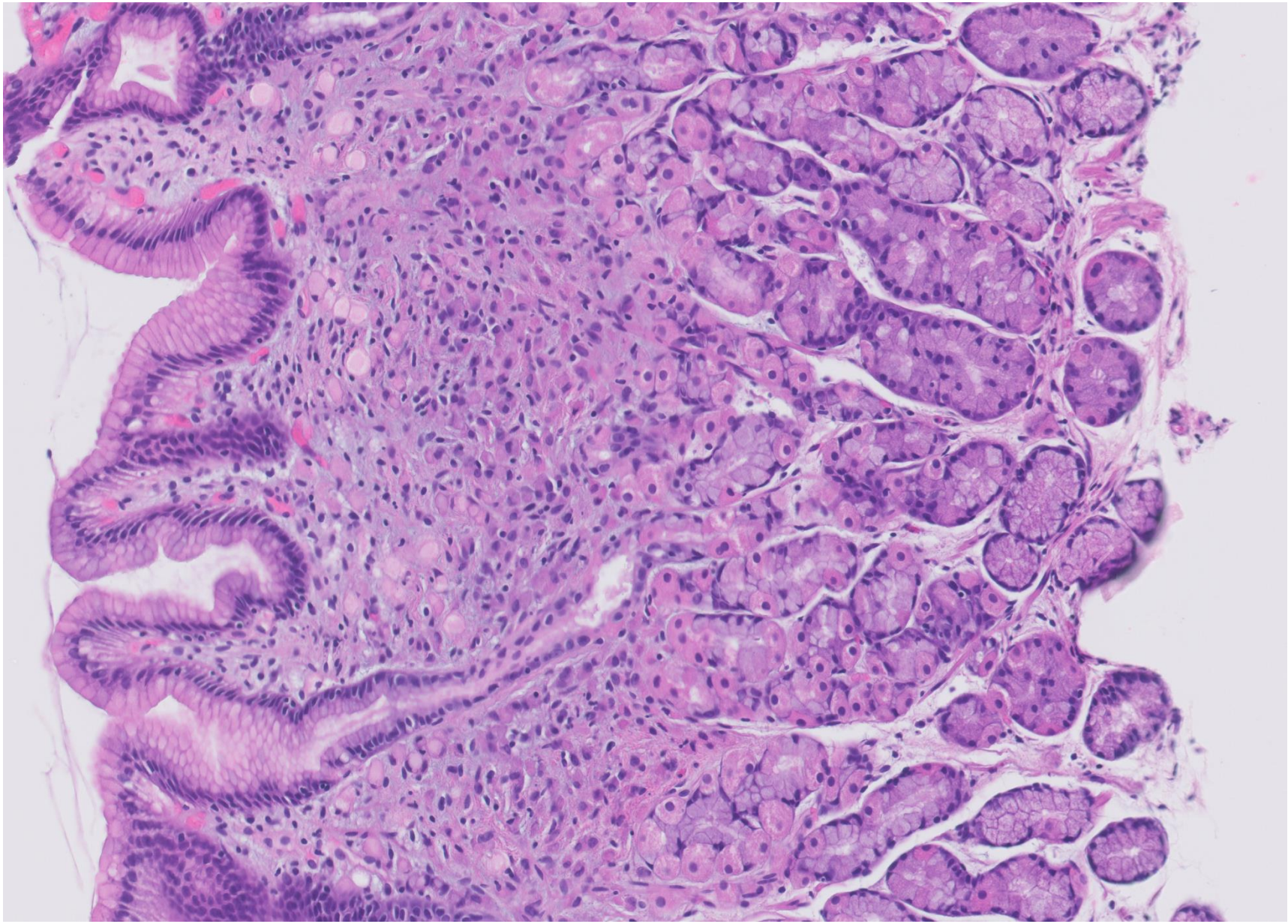
Ingrid P Vogelaar et al. J Med Genet doi:10.1136/jmedgenet-2015-103094

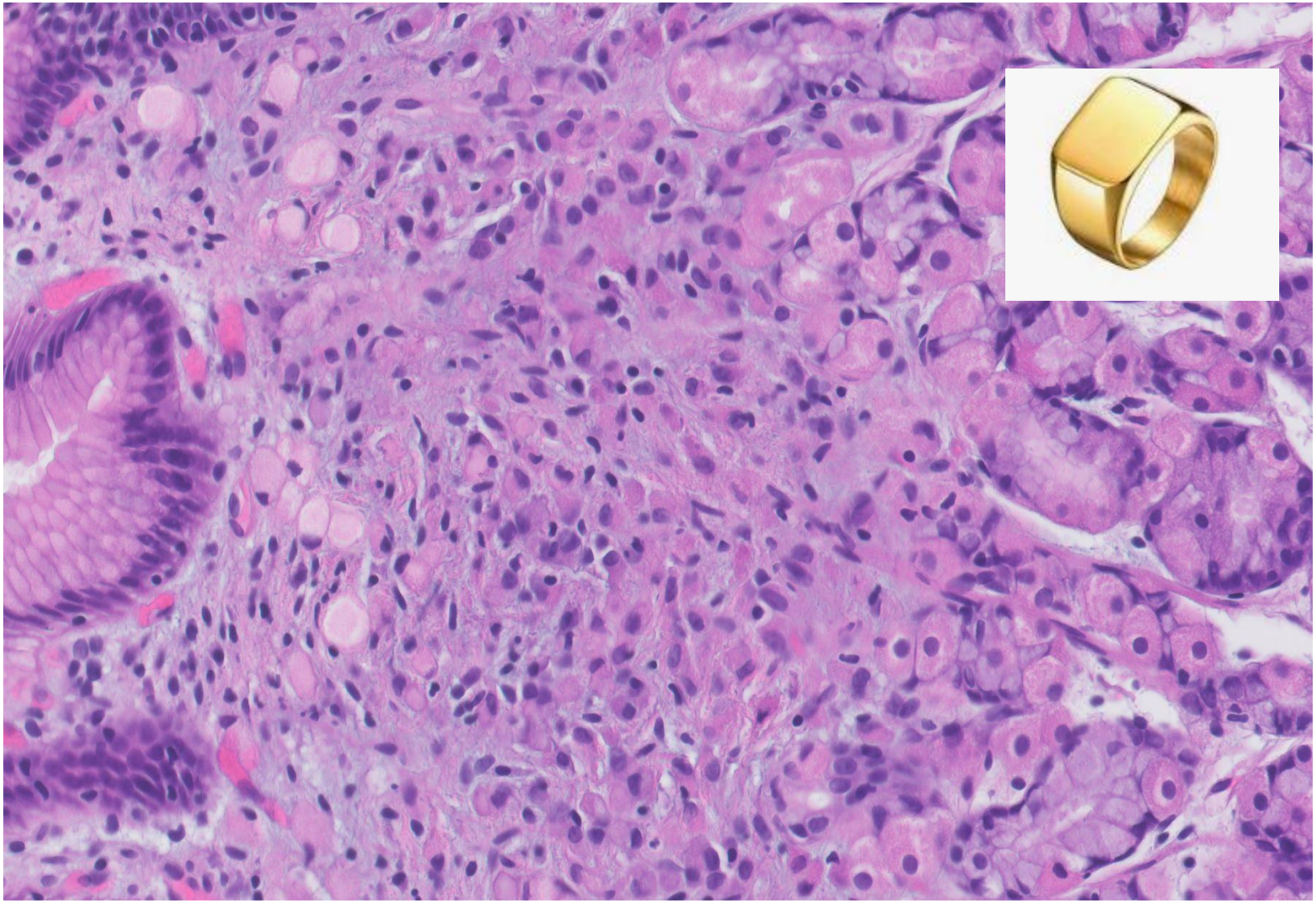
JMG

My Results

- Stomach, distal body greater curve, biopsy:

  - Invasive poorly differentiated carcinoma with signet ring cell involving one of 5 fragments.

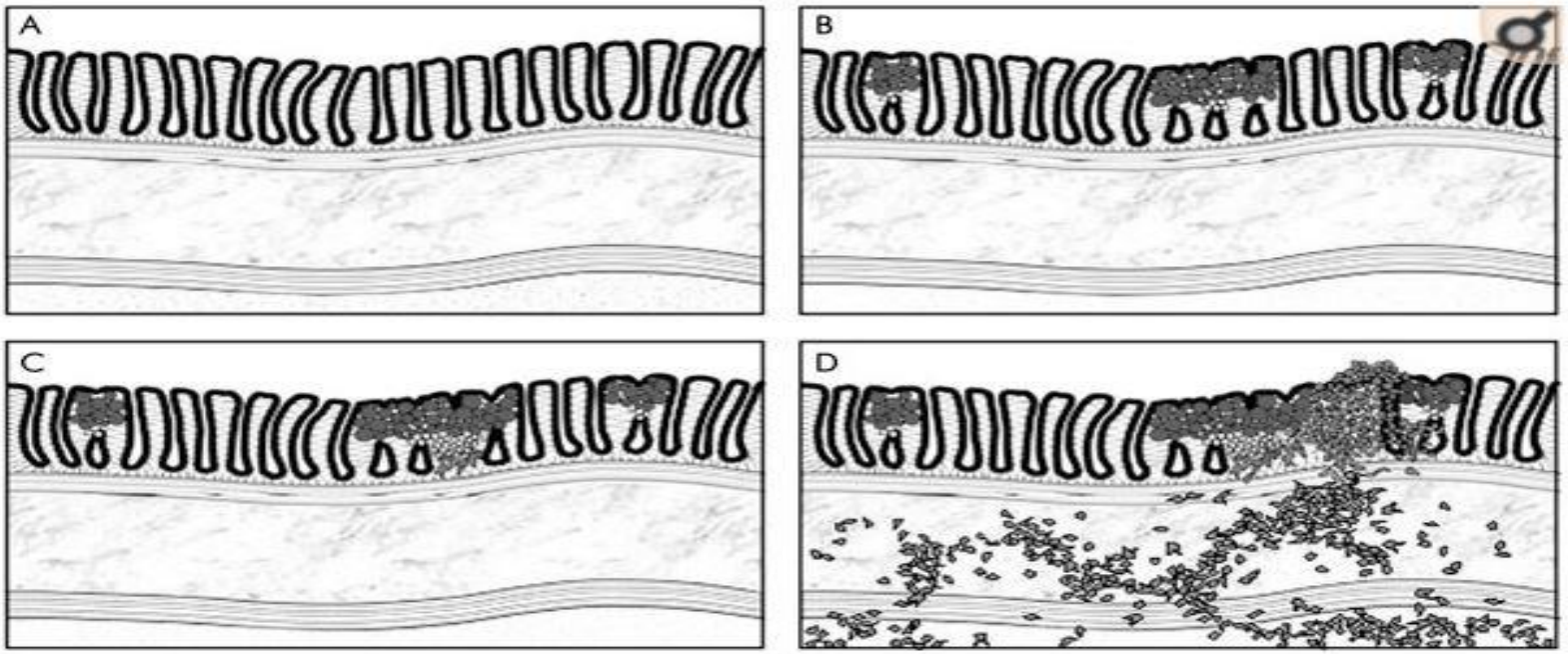




Histology

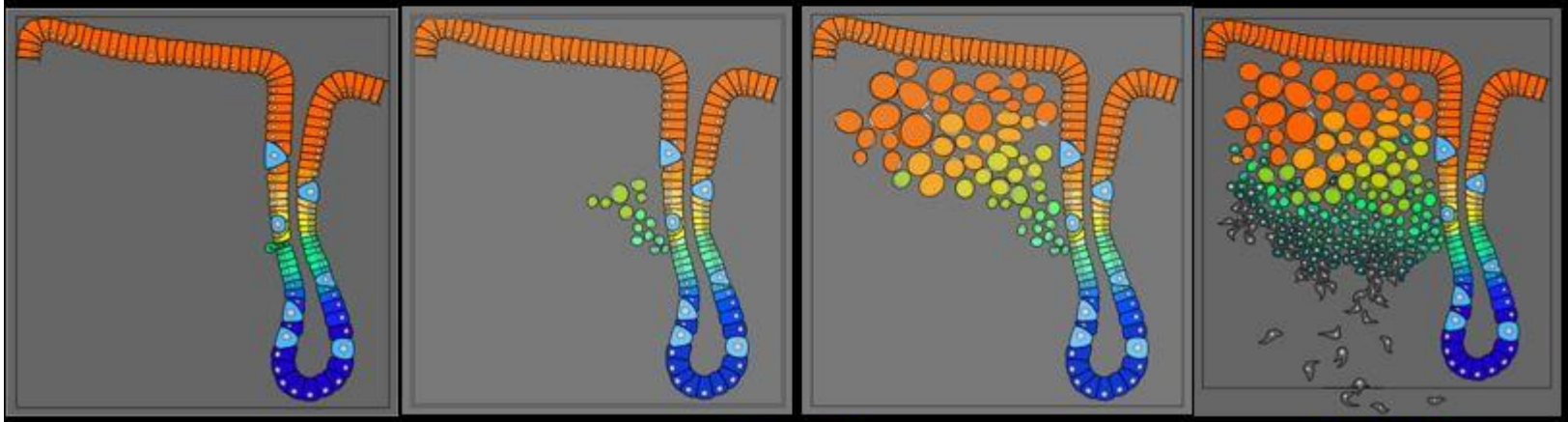
- Positive biopsy results show signet ring cells.
- Biopsies should be stained for H&E at 3 levels and periods acid-Schiff-diastase (PAS-D) as standard.
- Nearly all gastrectomies exhibit tiny foci of SRCC or in-situ ring cells.
- T1a carcinoma

Tumor Stages of HDGC



- **A** – normal gastric body mucosa; **B** – the first apparent disease stage in HDGC is multiple, minute foci of SRCC confined to the gastric mucosa (stage T1a). SRCs are the predominant cell type in these tumours, are typically located in the superficial mucosa underneath an intact surface epithelium and are mitotically inactive. Less differentiated and proliferating cancer cells are found in small numbers deep to the SRCs and are physically close to the gastric neck region; **C** – larger foci can acquire an increased amount of poorly differentiated cancer cells. These cells often have a fibroblastoid appearance consistent with an induction of an epithelial-mesenchymal transition; **D** – invasion through the muscularis mucosae and muscularis propria involves poorly and de-differentiated cancer cells. While the proliferative activity of stage T1a cancers is very low, more advanced cancers (≥ T1b) have a markedly increased proliferation rate.

HDGC life history



Stage T1a

>Stage T1a

- 2nd *CDH1* hit
- Division out of the plane

- Indolent
- Genetically simple

EMT/additional mutations

EMT: epithelial mesenchymal transition

Gastrectomy

- Prophylactic gastrectomy should be strongly advised in carriers of a proven pathogenic germline CDH1 mutation
- Typical timing is between age 20-30 although some consideration should be given to family phenotype i.e. age of onset
- 5 year survival rates only 30%

Endoscopic surveillance

- Gastrectomy preferred
- Timing concerns
- Inability to have a gastrectomy
- Concern
  - Once lesions are visible, cancer may be advanced
  - Multiple T1a foci of cancer

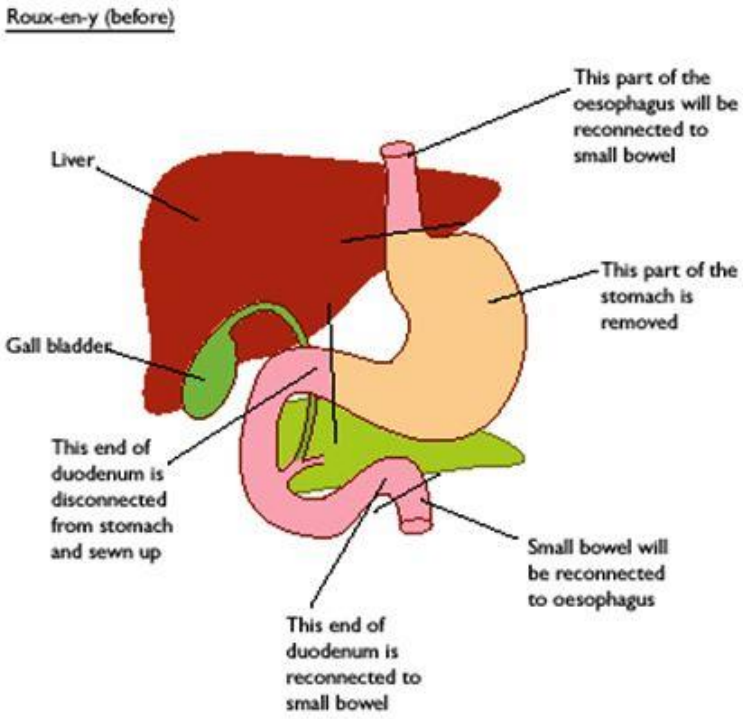
Mastectomy

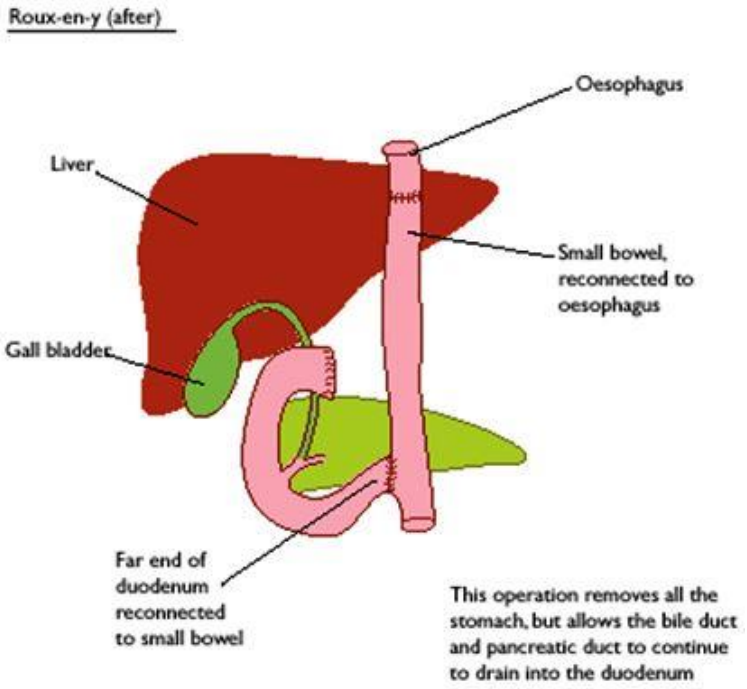
- Lobular breast cancer lifetime risk is 42%.
- Consider family pedigree
- Lobular breast cancer harder to detect with routine mammogram.
  - Consider yearly MRI with mammogram for monitoring.
  - Imaging to start at age 30.

Gastrectomy Operation

- Total gastrectomy with Roux-en-Y reconstruction, ensuring jejunioejunal anastomosis is at least 50cm distal to the esophagogastric anastomosis, to reduce the risk of biliary reflux.
- Jejunal pouch is not found to help long term.
- Open vs laproscopic.
- Typically feeding tube is not placed +/- drain tube.

Gastrectomy





Gastrectomy Before & After

Complications

- Leak
- Stricture
- Bleeding or infection
- Routine complications of gastric bypass or weight loss surgery

Postgastrectomy symptoms

- Dumping syndrome – early and late
- Lactose intolerance
- Fat malabsorption
- Small bowel bacterial overgrowth
- Dysphagia
- Change in response to alcohol
- Mineral and electrolyte deficiencies – iron, b12, folate, trace elements, calcium.
- Osteoporosis
- Bile reflux

Postgastrectomy screening

- Monitoring nutrition with lab
- Screening colonoscopy at age 40 (or 10 years younger than affected) and every 5 years.
- EGD one year after and periodically

Changes in eating required

- Loss of hunger
- Chew food well
- Slow down
- Eat more frequent
- Less quantity
- High nutritional foods/high calorie

Supplements

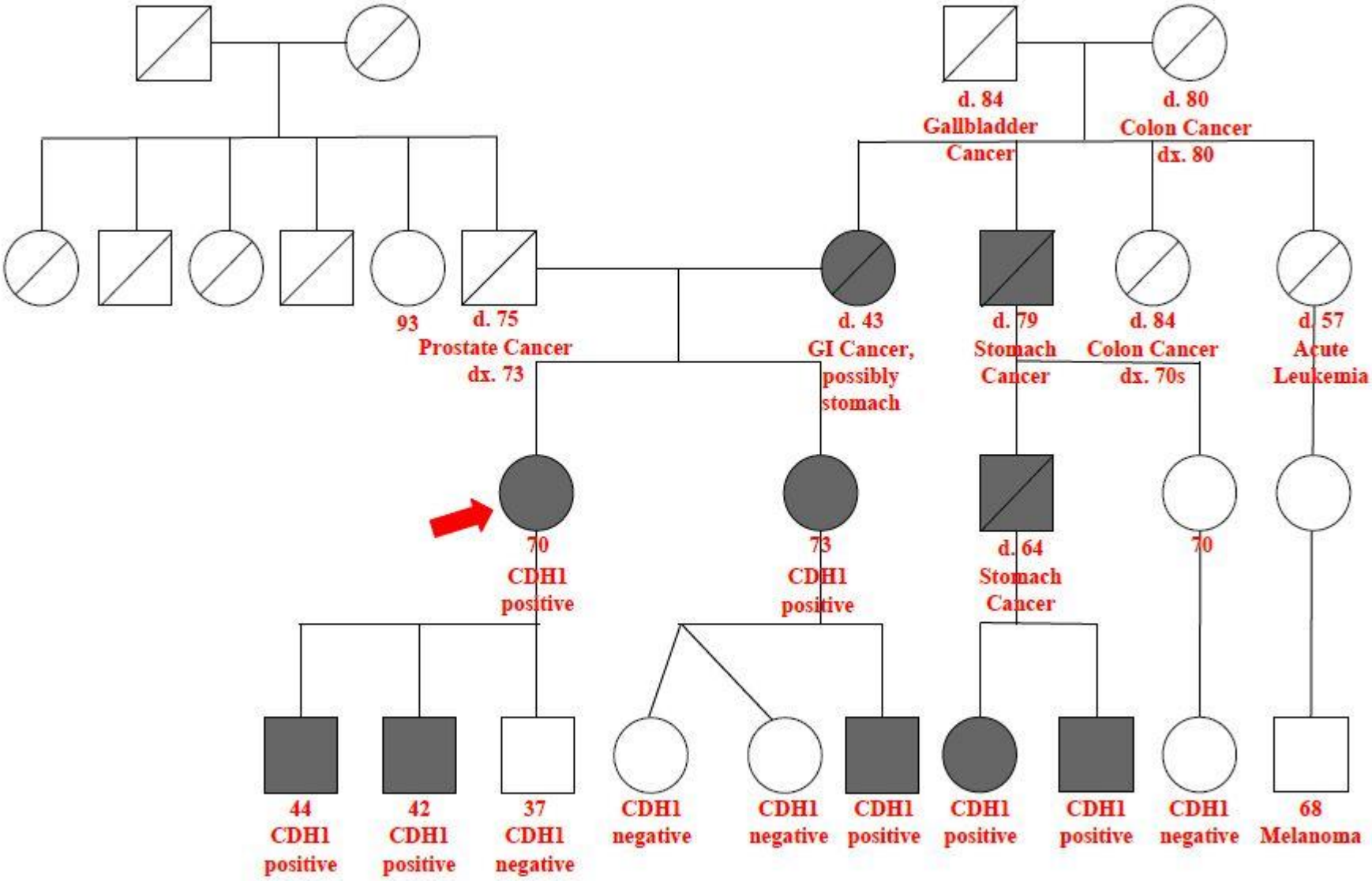
- Similar to Gastric-bypass patients
- B12- sublingual or injection
- MVI
- Vitamin D
- Others – calcium (citrate), iron, pancreatic enzymes, biotin
- Avoid extended release meds
- Consider liquid, dissolvable due to a lack stomach acid for absorption

Back to the story…

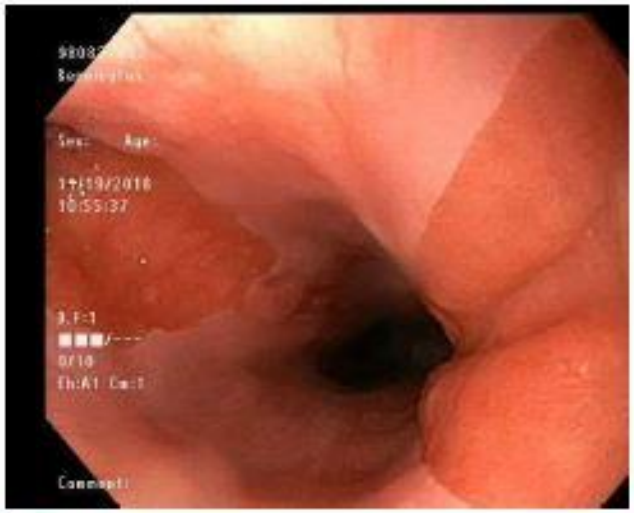
- Open total gastrectomy surgery Oct 7th with Dr. Sam Yoon and Memorial Sloan Kettering in NYC.
- Pain control with epidural pca pump – off narcotics in 3 days.
- No food or drink for 5 days followed by swallow study.
- Discharged on post-op day 6.
- Return home post-op day #10

Back to the story…

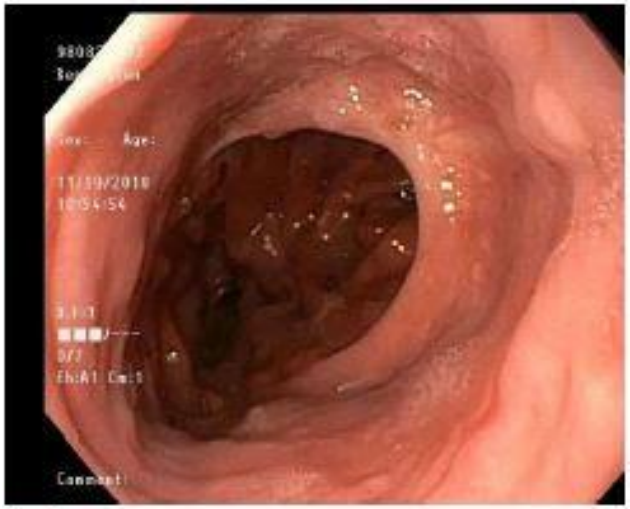
- Return to work at 6 weeks.
- Mom returned to work after 8 weeks.
- Most limiting symptom is fatigue and adjustment in nutrition.
- My family since diagnosis


d. 84
Gallbladder
Cancer
d. 80
Colon Cancer
dx. 80
93
d. 75
Prostate Cancer
dx. 73
d. 43
GI Cancer,
possibly
stomach
d. 79
Stomach
Cancer
d. 84
Colon Cancer
dx. 70s
d. 57
Acute
Leukemia
70
CDH1
positive
73
CDH1
positive
d. 64
Stomach
Cancer
70
44
CDH1
positive
42
CDH1
positive
37
CDH1
negative
CDH1
negative
CDH1
negative
CDH1
positive
CDH1
positive
CDH1
positive
CDH1
negative
68
Melanoma

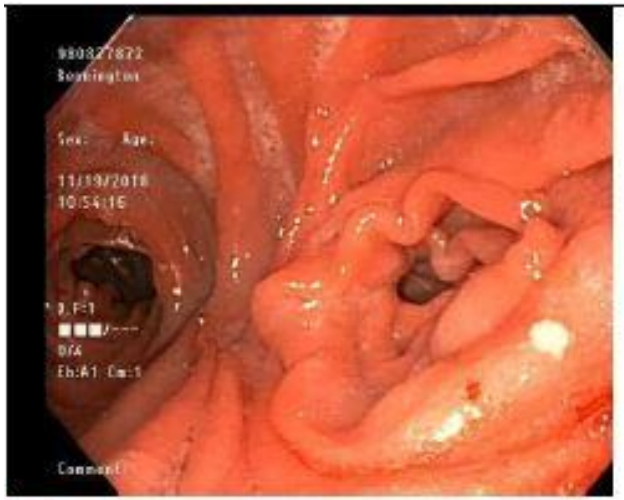
Follow-up Endoscopy



1 Upper Third of the Esophagus : Ectopic gastric mucosa

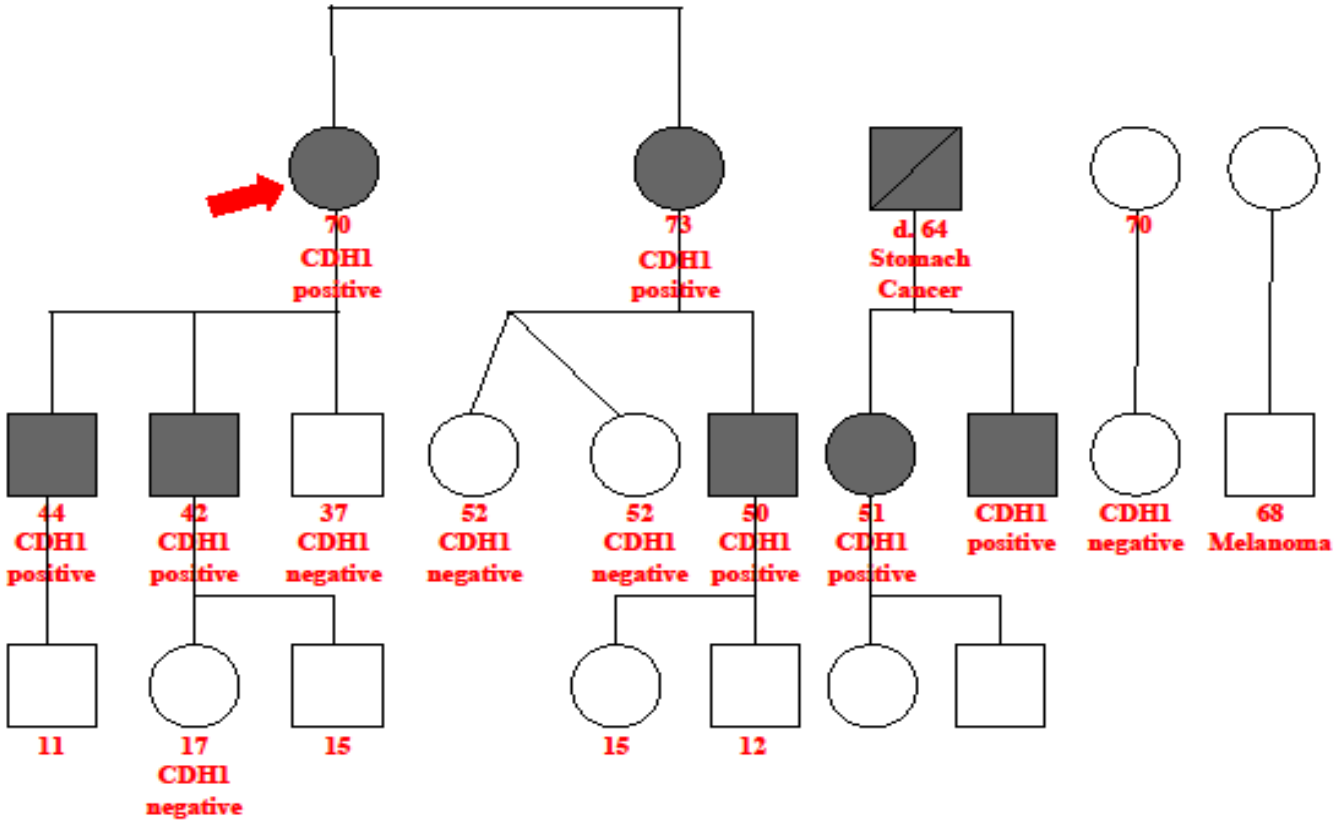


7 Esophago-Duodenal Anastomosis : Normal



8 Duodenum : Normal


Coca-Cola


70
CDH1
positive
73
CDH1
positive
d. 64
Stomach
Cancer
70
44
CDH1
positive
42
CDH1
positive
37
CDH1
negative
52
CDH1
negative
52
CDH1
negative
50
CDH1
positive
51
CDH1
positive
CDH1
positive
CDH1
negative
68
Melanoma
11
17
CDH1
negative
15
15
12

53113549

PATIENT COPY CONFIDENTIAL

Single Site Analysis

myRisk Genetic Result

MYRIAD myRisk® Hereditary Cancer | Powered by myVision

RECEIVING HEALTHCARE PROVIDER
Talya Greathouse, MD
1717 W Main St Ste 200
Newark, OH 43055

SPECIMEN
Specimen Type: Blood
Draw Date: Jun 11, 2018
Accession Date: Jun 18, 2018
Report Date: Jul 06, 2018

PATIENT
[redacted]

GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

TEST PERFORMED	RESULT	INTERPRETATION
CDH1 c.1064del (p.Leu355*)	Mutation Not Detected	This specific mutation was not identified in this patient.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

ADDITIONAL INFORMATION

GENES ANALYZED

Analysis was performed on the mutation(s) specified above.

The following comment applies only if this patient was tested for a variant that was originally detected in a laboratory other than Myriad. Laboratories sometimes differ in the way they name genetic variants, and there are also cases where the ability to detect a variant could differ based on testing technology. Rare instances can occur where these differences result in a patient receiving an incorrect result. Any concerns about this possibility can be addressed by submitting a specimen to Myriad from the relative in whom the variant was originally detected. If you would like to discuss this option, please contact Myriad Medical Services at 1-800-469-7423 X 3850.

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: The patient test result was negative for the mutation(s) specified. In most cases, this result means the patient is not at increased risk for hereditary cancer related to the test performed. In certain cases, personal and family history analysis may identify other cancer risks, and additional genetic testing may be appropriate. Therefore, a myRisk Management Tool is not provided. This patient is considered a true negative for the familial mutation only if the originally tested family member's mutation was confirmed to be germline in origin (versus somatic, see the family member's original test result). Please contact Myriad Medical Services at 1-800-469-7423 X 3850, if you have questions.

Analysis Description: The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications/) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. The interpretation of this test may be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant.

CLASSIFICATION DISCLAIMER

THE CLASSIFICATION AND INTERPRETATION OF ALL VARIANTS IDENTIFIED IN THIS ASSAY REFLECTS THE CURRENT STATE OF MYRIAD'S SCIENTIFIC UNDERSTANDING AT THE TIME THIS REPORT WAS ISSUED. VARIANT CLASSIFICATION AND INTERPRETATION MAY CHANGE FOR A VARIETY OF REASONS, INCLUDING BUT NOT LIMITED TO, IMPROVEMENTS TO CLASSIFICATION TECHNIQUES, AVAILABILITY OF ADDITIONAL SCIENTIFIC INFORMATION, AND OBSERVATION OF A VARIANT IN MORE PATIENTS.

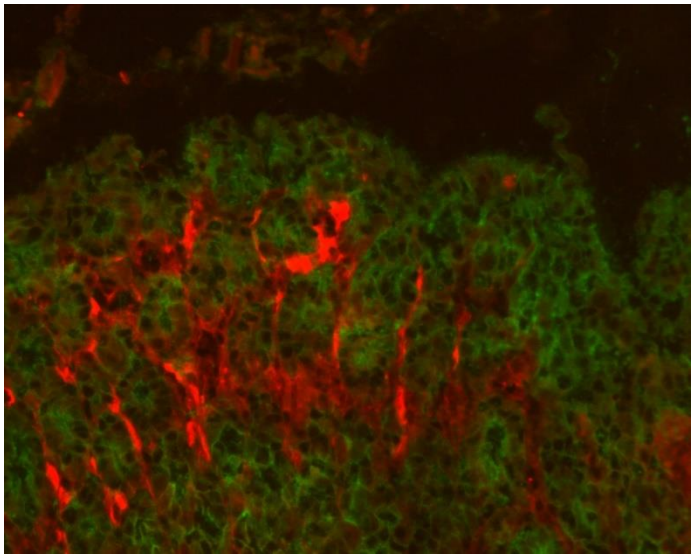
Future Research

- Mouse models being created with CDH1 gene knocked out.
- Starting 2019 will be starting drug trial.
- In-vitro

DGC mouse model

- CD44/Cre-*Cdh1*$^{loxP/loxP}$/Td-tomato$^{loxP/loxP}$

  -*Cdh1* deletion induced with tamoxifen



Stomach antrum: red cells are gastric glands with CDH1 knocked out

Candidate drugs to be tested on this model to see if they kill the red cells only -starting 2019

Top 5 reasons I like not having a stomach

5. Stomach jokes – “I lost my stomach,” I can’t stomach that.”…

4. No acid reflux because there is no acid

3. Difficult to have issues with obesity

2. Cheap date.. 1 drink maximum

And the #1 reason I like not having a stomach is…….

NO

STOMACH

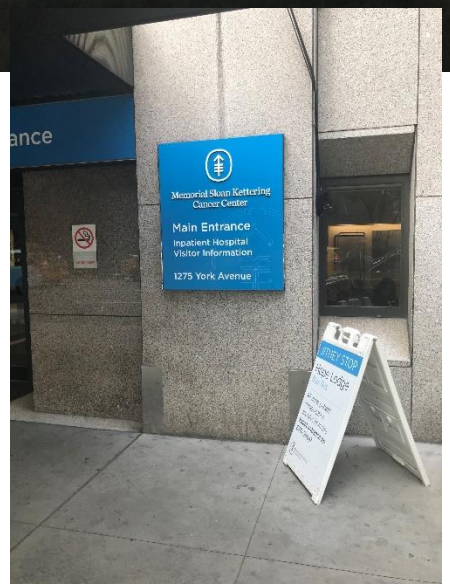
CANCER

My Team

Resources

- Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392:402–5.
- Van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carries. J Med Genet 2015; 52:361.
- Hebbard P, Schrader K. Hereditary diffuse gastric cancer- UpToDate. 2018.
- Chan A, Wong B. Epidemiology of gastric cancer –UpToDate 2017.
- Guilford P, Blair V, More H, Humar B. A short guide to hereditary diffuse gastric cancer. Hereditary Cancer in Clincal Practice. 2007; 183-194.
- Guilford P. No Stomach For Cancer: 2015 Spotlight on Gastric Cancer.
- No Stomach for Cancer website.

Thank You


Memorial Sloan Kettering Cancer Center
Main Entrance
Inpatient Hospital Visitor Information
1275 York Avenue


Indians