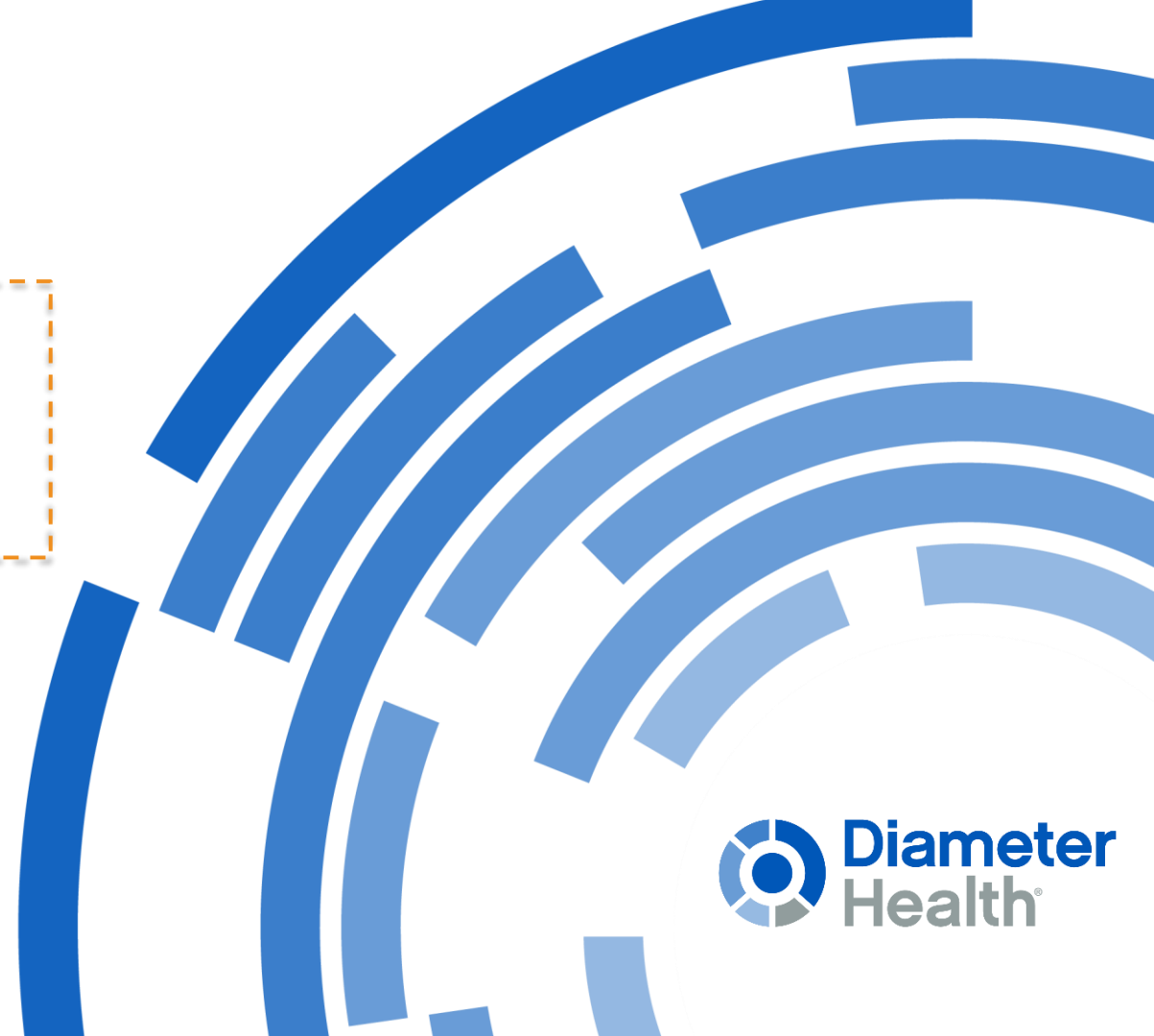
“Underwriting Between the Lines – How do we handle hunches, genetic quirks and zebras?”

Presented To:

Texas Wide Underwriting Conference

October 6, 2021



Diameter Health®


TWUC AGENDA
Wednesday, October 6th, 2021
12:00 – 01:00 LUNCH & NETWORKING OPPORTUNITY
$25.00 Grubhub gift card from TWUC & Sponsors
01:00 – 01:15 WELCOME TO TWUC
Jill Thompson, TWUC President
01:15 – 02:00 UNDERWRITING NUANCES OF BREAST CANCER PROGRESSION USING MEDICAL DATA
Scott Collier, Milliman
02:00 – 02:15 BREAK & ANNOUNCEMENTS
02:15 – 03:00 NAVIGATING IN THE WORLD OF FOREIGN NATIONAL INSURANCE
Cindy Davis, FALU, FLMI, ACS
Assistant Vice President, Senior Underwriting Consultant, National Financial Partners
Mike Hesse, FALU, FLMI, ARA
Vice President, Chief Underwriter, RGA
03:00 – 03:15 BREAK & ANNOUNCEMENTS
03:15 – 04:15 UNDERWRITING BETWEEN THE LINES - HOW DO WE HANDLE HUNCHES, GENETIC QUIRKS AND ZEBRAS?
Paulo B. Pinho, MD
Vice President & Medical Director of Innovation, Diameter Health
04:15 – 04:30 CLOSING REMARKS
Jill Thompson, TWUC President
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Today's Presentation

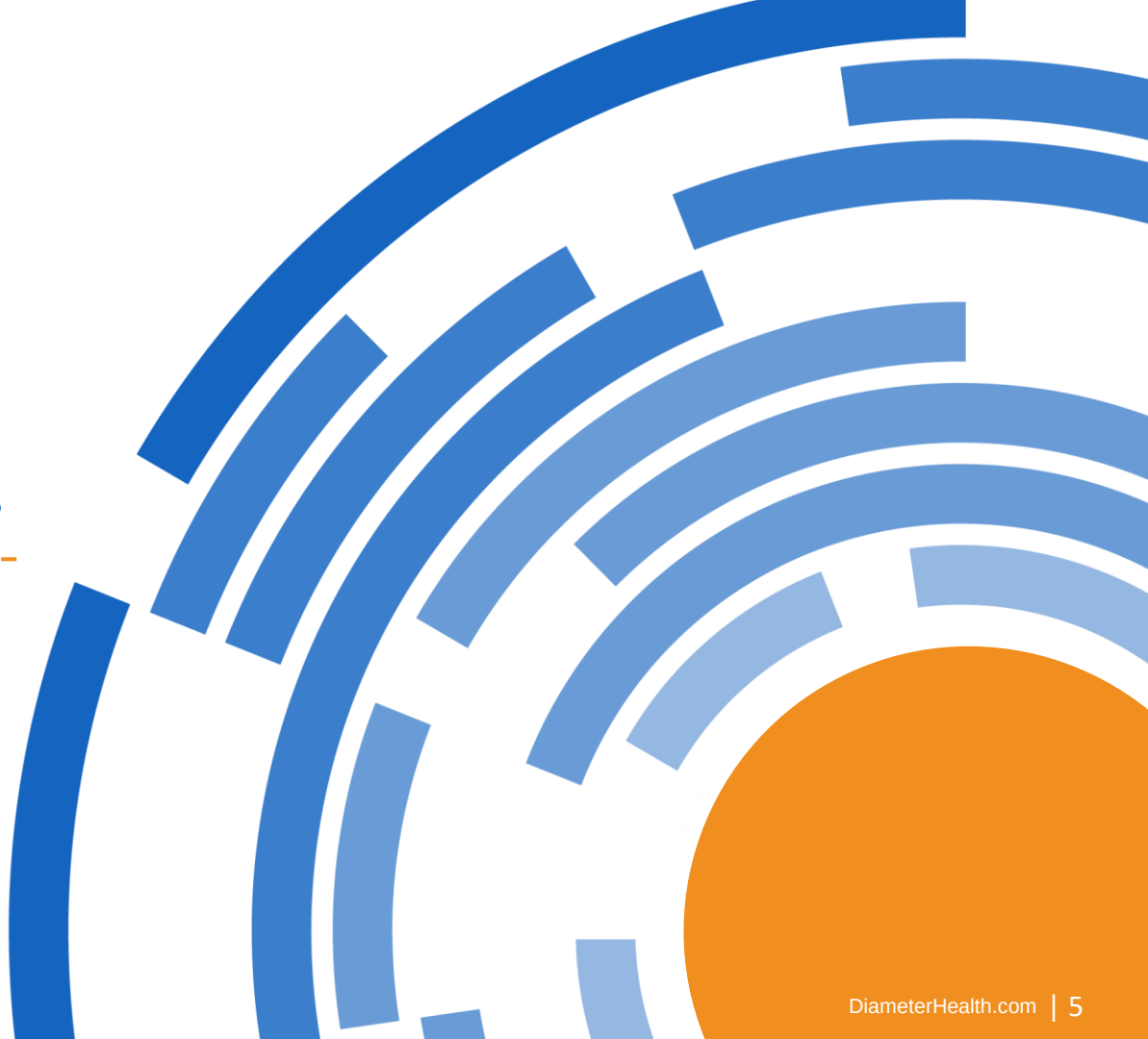
1. Hunches – an AS case, 1 febrile seizure case
2. Genetic Quirks – HCM, the other PKD, Familial Colon Cancer (time permitting)
3. Zebras – Autism, Sarcoid/Silicosis
4. Questions

Diameter Health

Disclaimer

- Cases used in this presentation are real and not fictional
- AND
- No zebras, underwriters or medical directors were harmed in the making of this PowerPoint deck

Hunches



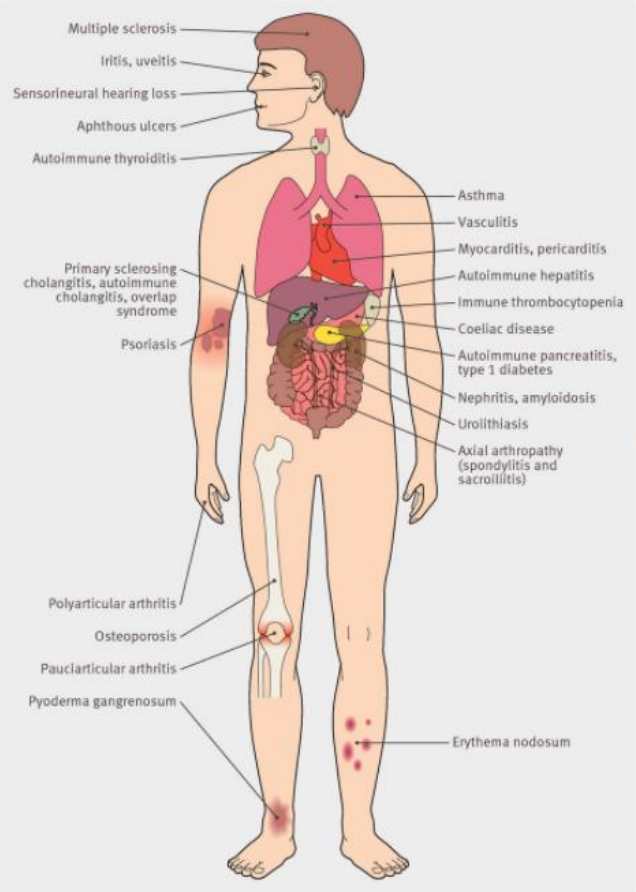
Hunch #1

- *Doctor, this is a male 44 years old smoker, 5'11" 175lbs. He has a rated history of Crohn's and Ankylosing Spondylitis. I would simply need your opinion on the abdominal US results noted on page 37 and the GI follow up on page 33 of the APS document:*
  - *Ileo-cecal Crohn's stable for many years, terminal ileum resection in 2006 And R hemicolectomy in Oct 2008, due to fistulas.*
  - *Ankylosing spondylitis stable and doing well for many years treated with Imuran.*
- *- p.37: 08-2018, noting mild splenomegaly at 14.2cm (NORMAL 12 cm), diffuse hep steatosis, bottom of page mentions he was told of the results on Sept 14, 2018 and advised to discuss with his gastroenterologist*
- *- p.33: the notes indicate that a CBC done in July 2018 noted WBC's at 2.7 and the GI specialist seems to note Leukopenia due to Imuran and suggested he reduce his dose. Additionally there is slight elevation in total bilirubin in 2018*
- *There are no labs done since and no follow up with MD because of the fact that he has felt well.*
- ***In your opinion should we ask for a repeat abdominal US to further assess the mild splenomegaly (14.2cm) noted on the abdominal US in 2018?***

Imuran hematologic side effects

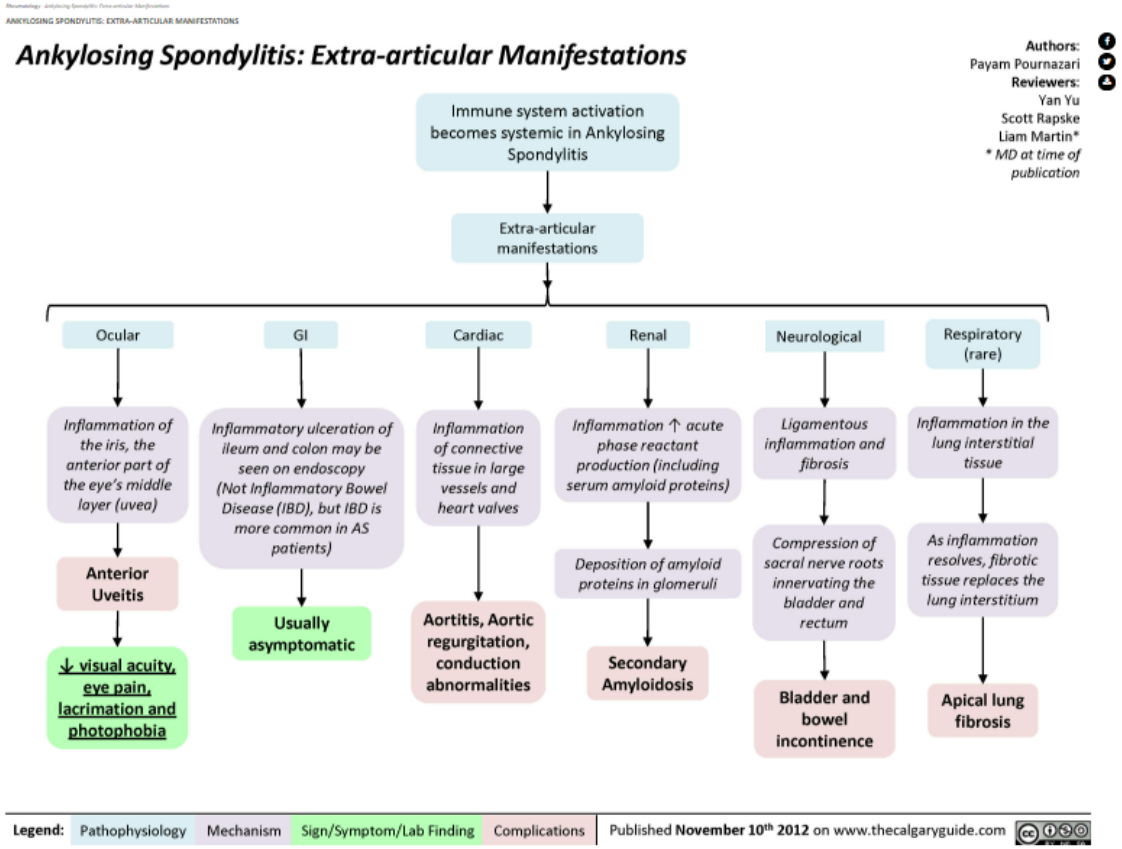
- Marrow suppression
  - Leukopenia in up to 27 % of patients
  - Mild leukopenia usually responds to a reduction in the daily dose of AZA
- Malignancy risk
  - small increased risk of malignancy
  - increase in hematologic malignancies in patients with SLE

Extraintestinal Crohn's



Extraintestinal manifestations and associated autoimmune disorders in patients with Crohn's disease. Adapted from Baumgart and Sandborn 7

Extraarticular AS



Hunch #1 – Poll Question

1. Can we offer knowing that there is splenomegaly and steatosis?
2. Does the Leukopenia bother you?
    1. Would like a CBCD
    2. Would like to know the status of Imuran
    3. Leukopenia in the presence of splenomegaly is worrisome
    4. All of the above
    5. I am reassured that the doctor felt it was due to Imuran
3. Do we need any other labs? Imaging?
    1. I'd like a repeat US – would like to see liver and spleen
    2. I'd like a Comprehensive Metabolic Panel to look at LFTs
    3. I'm fine with what we have now, I would offer
    4. I'm fine with what we have now, would decline now

Hunch #2

- *Dear Doctor, Please interpret the ECG. Client now age 4. ECG was done during investigation for complex febrile seizures in 7/19, when he was 2 years old. We postponed with reconsideration in three years.*
- *4-year-old with likely febrile seizures described as complex. There is evidence of normal development through 2019, nothing beyond that.*
- *We maintain PP and r/c in 3 years.*

- I reviewed the pediatric EKG and it was normal

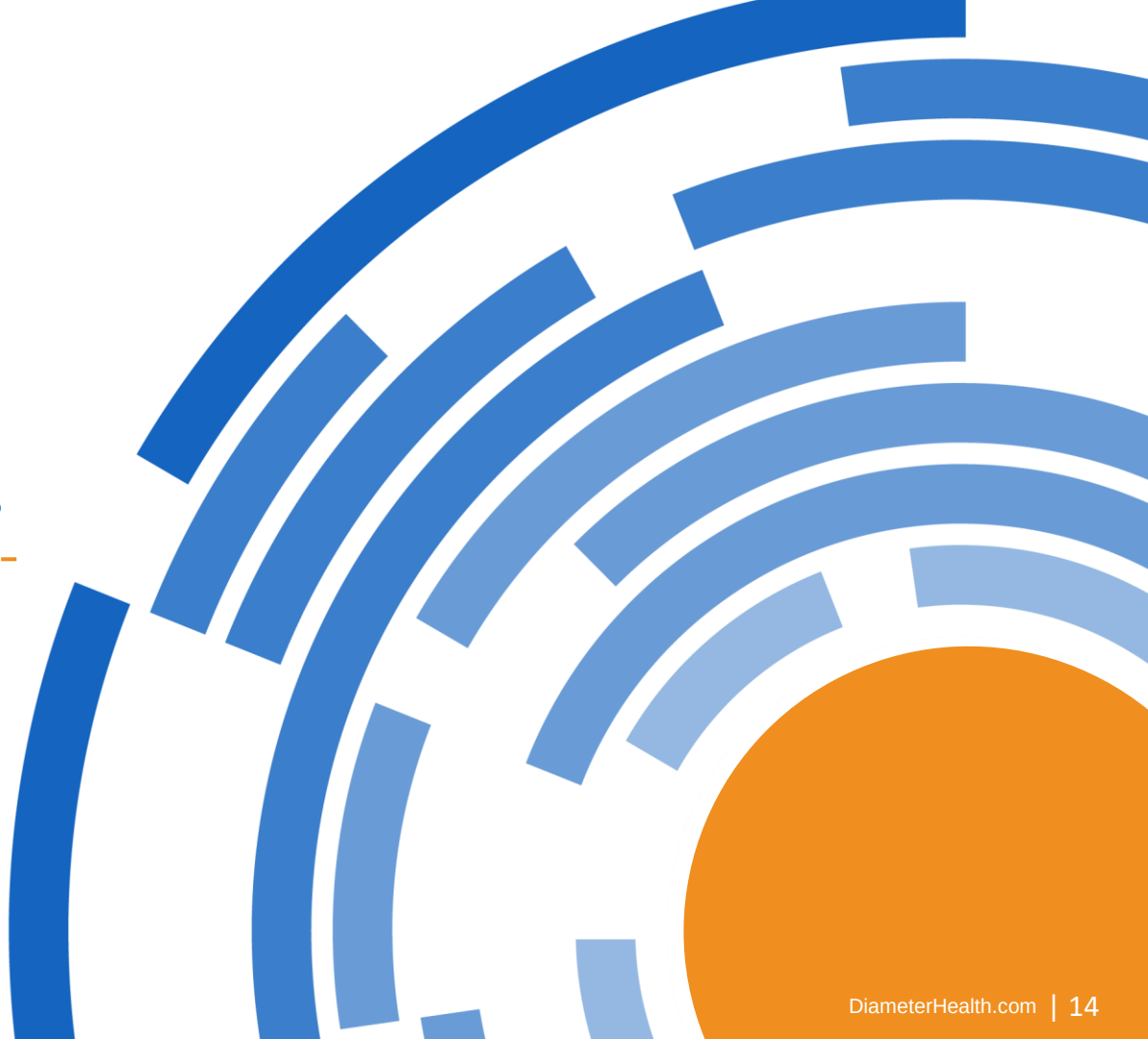
Febrile Seizures

- Age dependent
- 6 months to 6 years
- M>F 1.6:1
- Temp > 38 degrees Celsius
- Occurs in 2-4% of children in that bracket
- Simple – generalized less than 15 minutes and non-recurring
  - Eventual recurring in 1/3 of children
  - Epilepsy risk is slightly higher than general
- Complex – focal, prolonged or multiple in the 1st 24 hours
  - Higher risk of recurrence and future epilepsy
  - Todd's paralysis
- Risk factors

Hunch #3 – Poll Question

1. Can we offer now?
2. Do we want to postpone for 3 years for the febrile seizures?
3. What information would you need to feel comfortable with an offer now?
    1. Clinical history
    2. Clinical history and developmental assessment
    3. Clinical history, developmental assessment, EEG
    4. Clinical history, developmental assessment, EEG and MRI of the brain

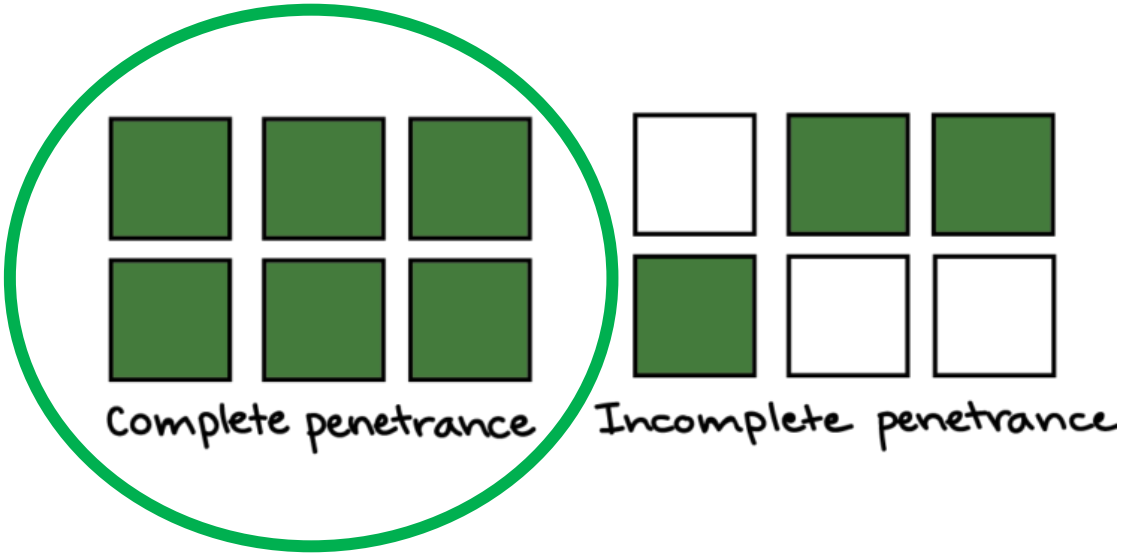
Genetic Quirks



Genetic Quirk #1

- *Male 28-year-old for 500k*
- *Family history of hypertrophic cardiomyopathy diagnosed in father at age 28. Father died at age 50 of complications from cardiomyopathy*
- *1 brother died of complications from cardiomyopathy and 2 others with phenotypic evidence*
- *the client says he is being followed by a cardiologist and that the tests are normal*
- *last follow-up 1/2021 according to client*
- *recommended follow-up every 2 years*
- *if the tests are normal for him at 28 years old, could he develop cardiomyopathy in the future?*
- *your opinion please, refusal as is or possible rated offer. thank you*

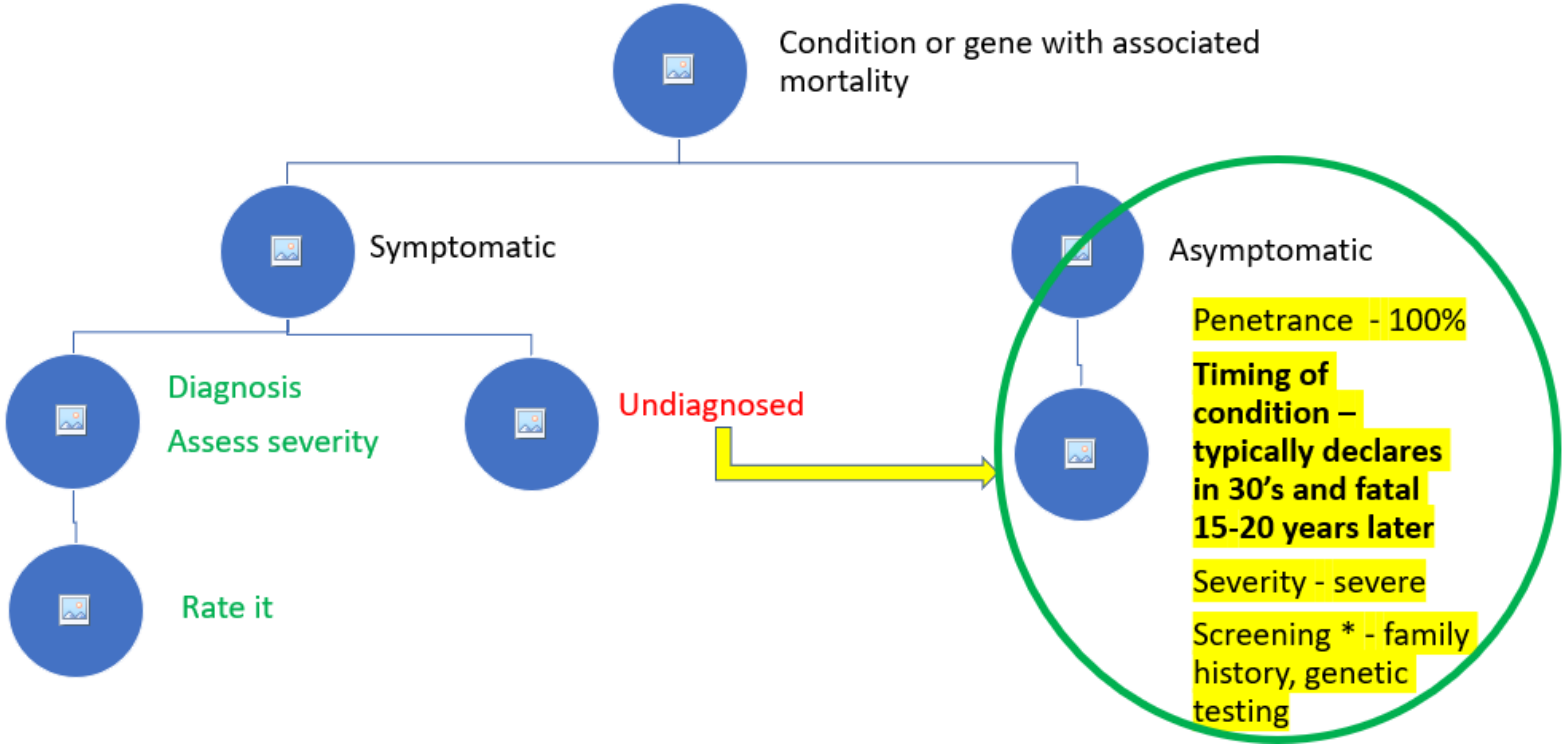
Genes (AD)-Genotype → **Penetrance** → Phenotype



How Huntington's is different

- 30-year male without significant past medical history applying for $1,000,000 in VUL coverage.
- His mother was diagnosed with Huntington's Chorea at age 40 when she began to have muscle fasciculations. She was adopted and did not know her biological parents.
- He is completely asymptomatic.

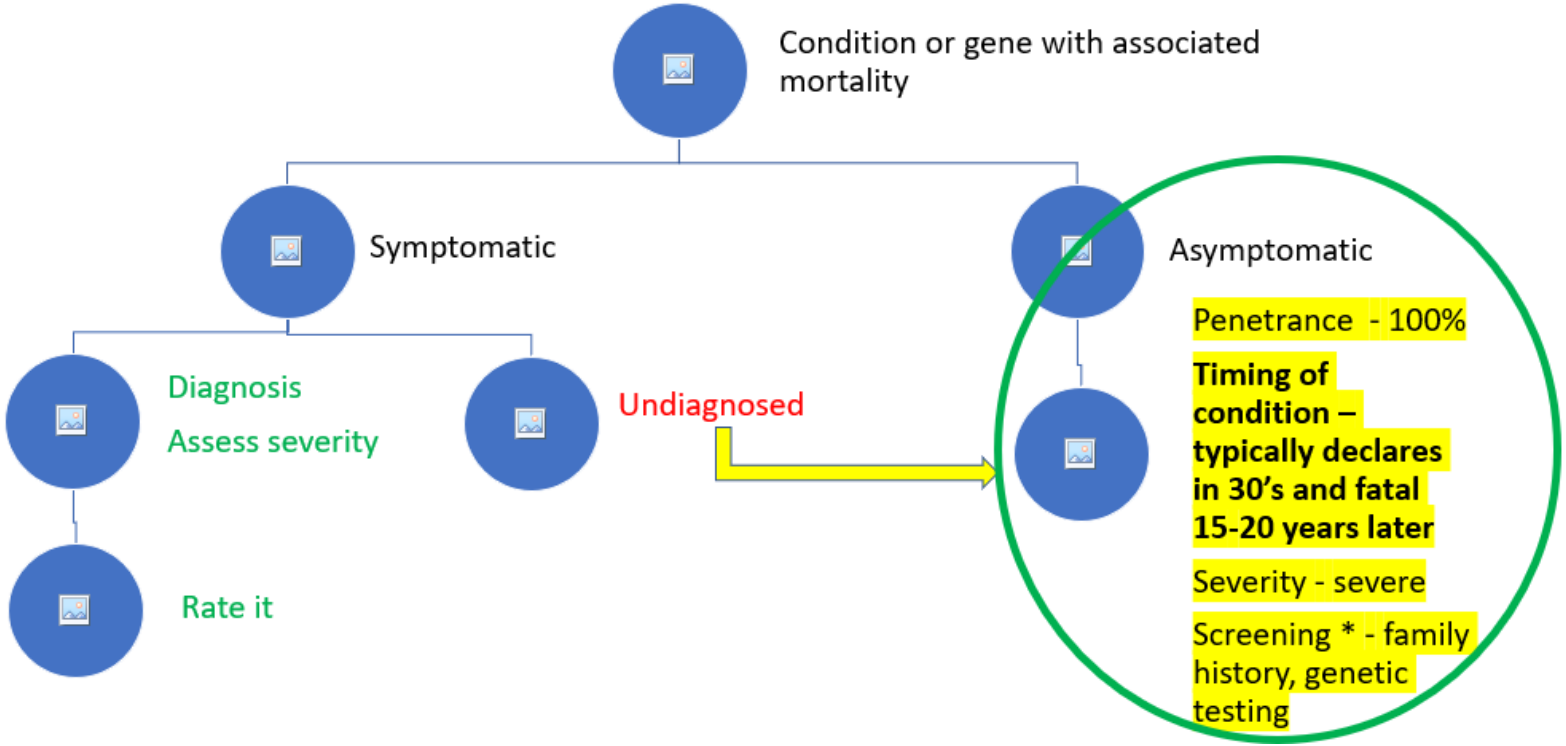
Underwriting Approach – Huntington's



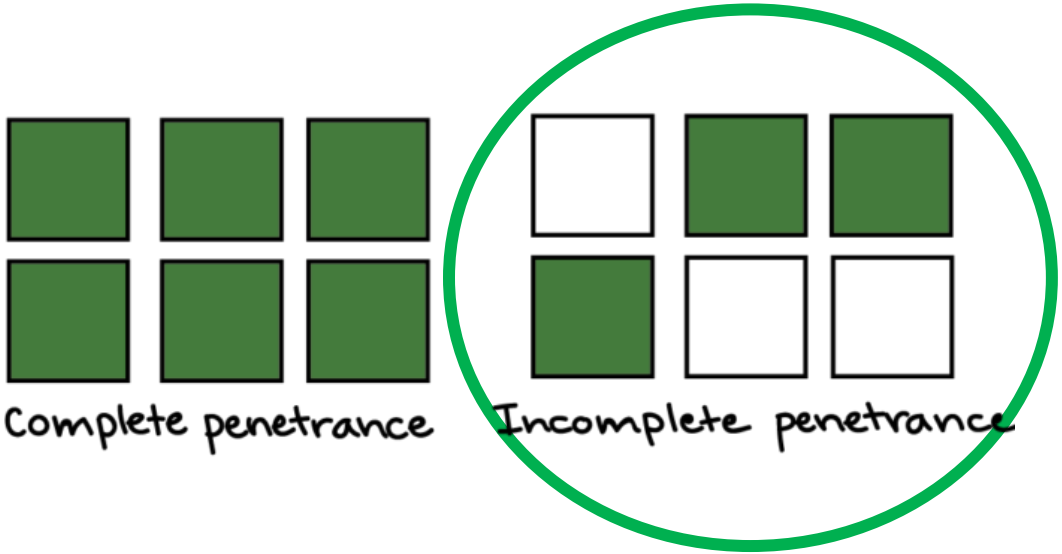
How Huntington's is different

- 60-year male $1,000,000 in VUL coverage
- PMH: no admissions
- His mother was diagnosed with Huntington's Chorea at age 40 when she began to have muscle fasciculations. She was adopted and did not know her biological parents.
- He is completely asymptomatic.

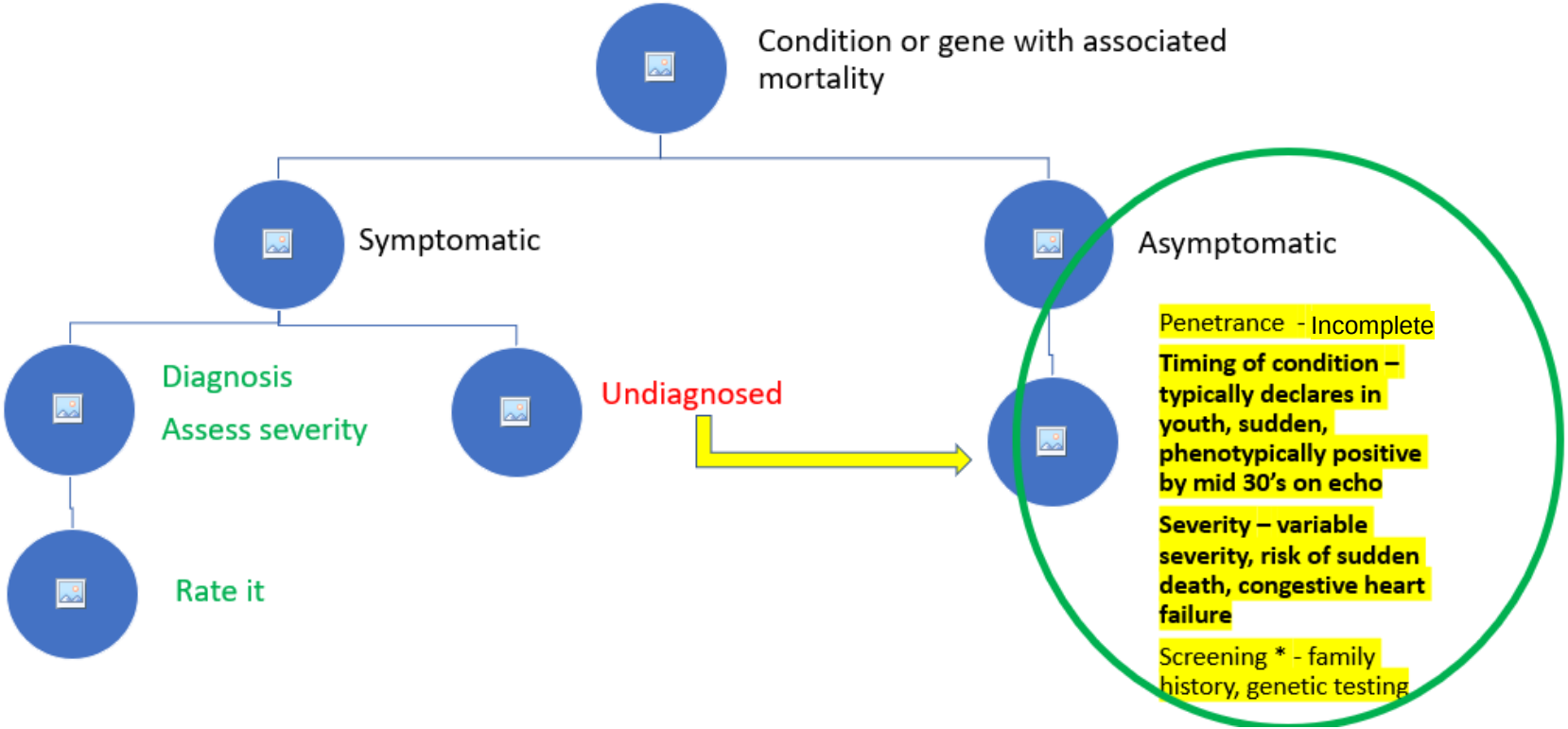
Underwriting Approach – Huntington's



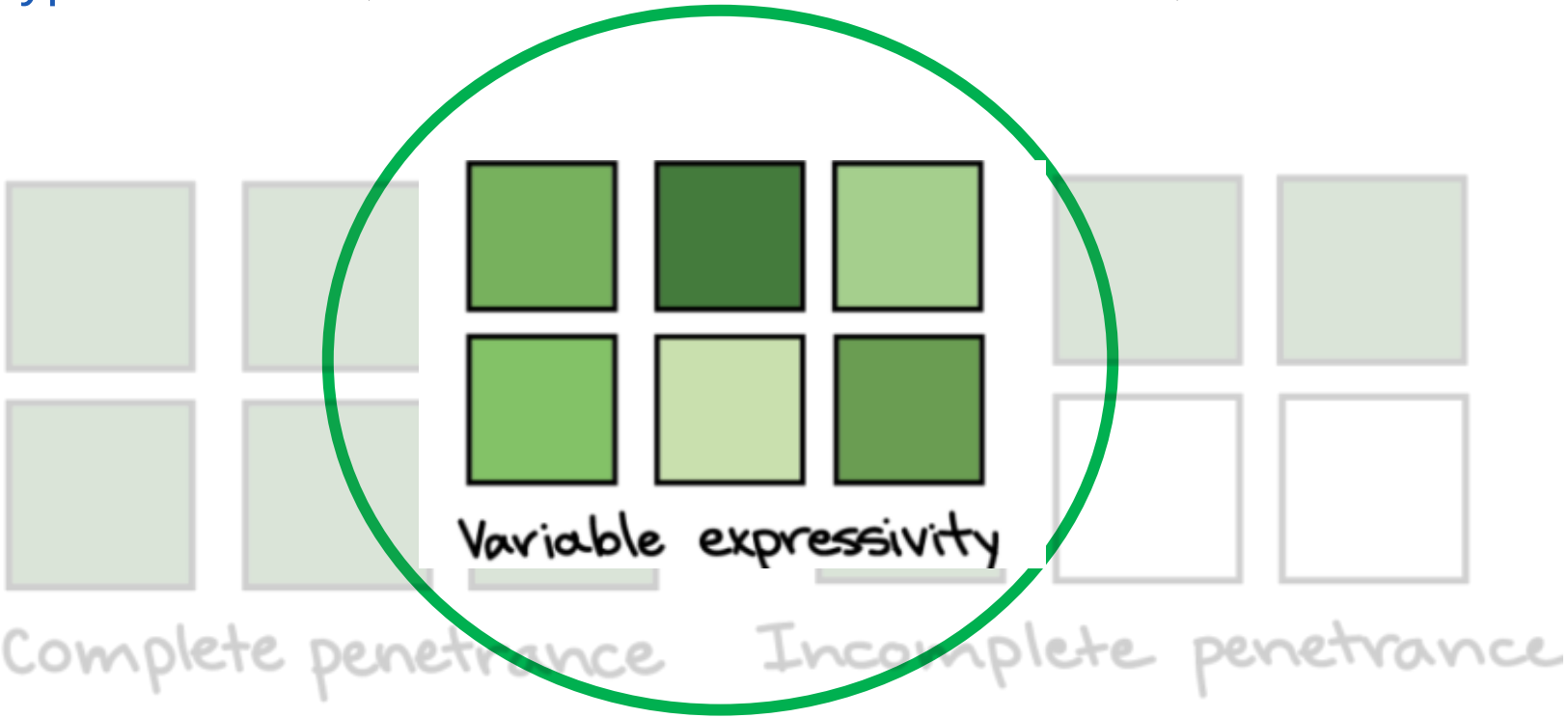
Genes (AD)-Genotype → **Penetrance** → Phenotype



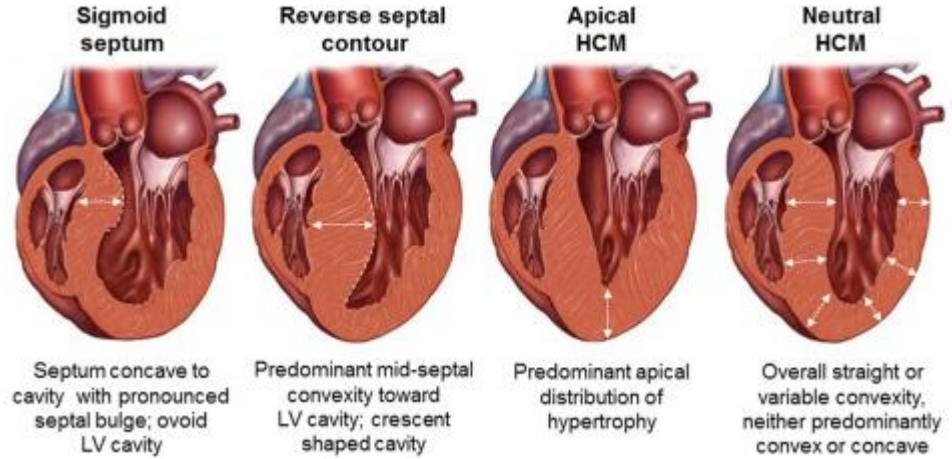
Underwriting Approach – Hypertrophic Cardiomyopathy



Genes (AD)-Genotype Phenotype → Penetrance - **Variable Expressivity** →

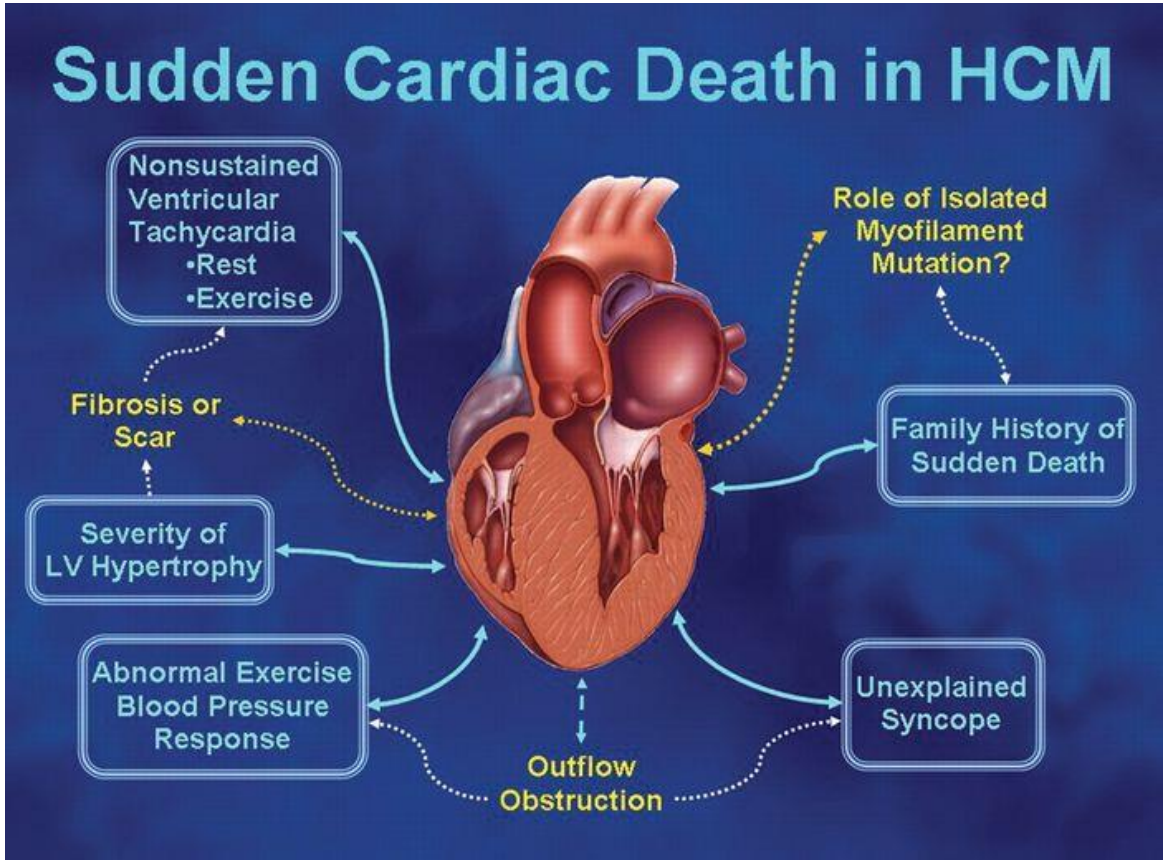


What's the deal with HCM?



www.sciencedirect.com/science/article/pii/B9780128018125000056

Causes of Death in HCM – It's a SADD disease



www.labroots.com/trending/cardiology/3965/stem-cell-model-hypertrophic-cardiomyopathy

Genetic Quirk#1- Poll Question

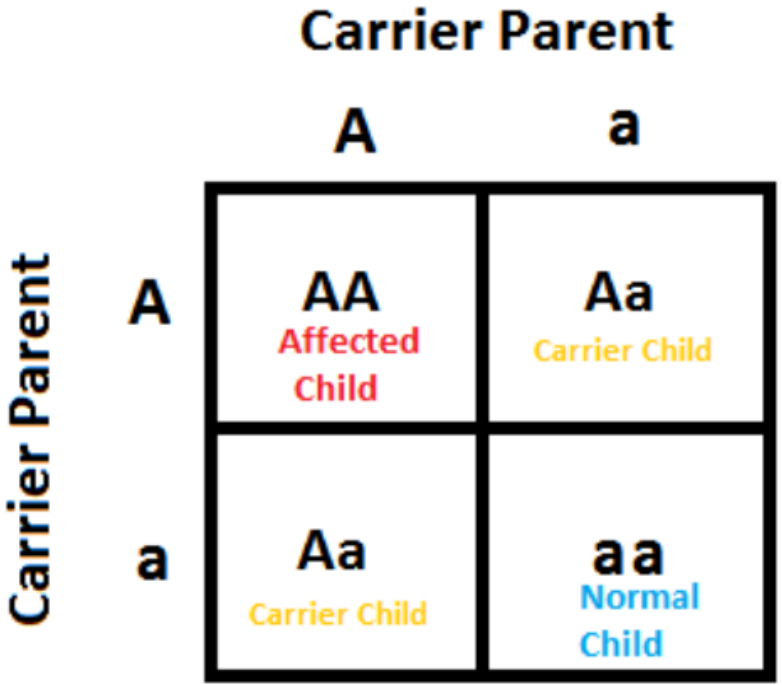
1. Do you offer now?
2. When would you feel comfortable offering?
    1. Now
    2. After 30 because that's when these cases declare themselves most by
    3. After 35 – worried about family history, especially early death and symptoms
    4. Never
3. What do you need to make an offer?

Genetic Quirk #2 - Poll Question

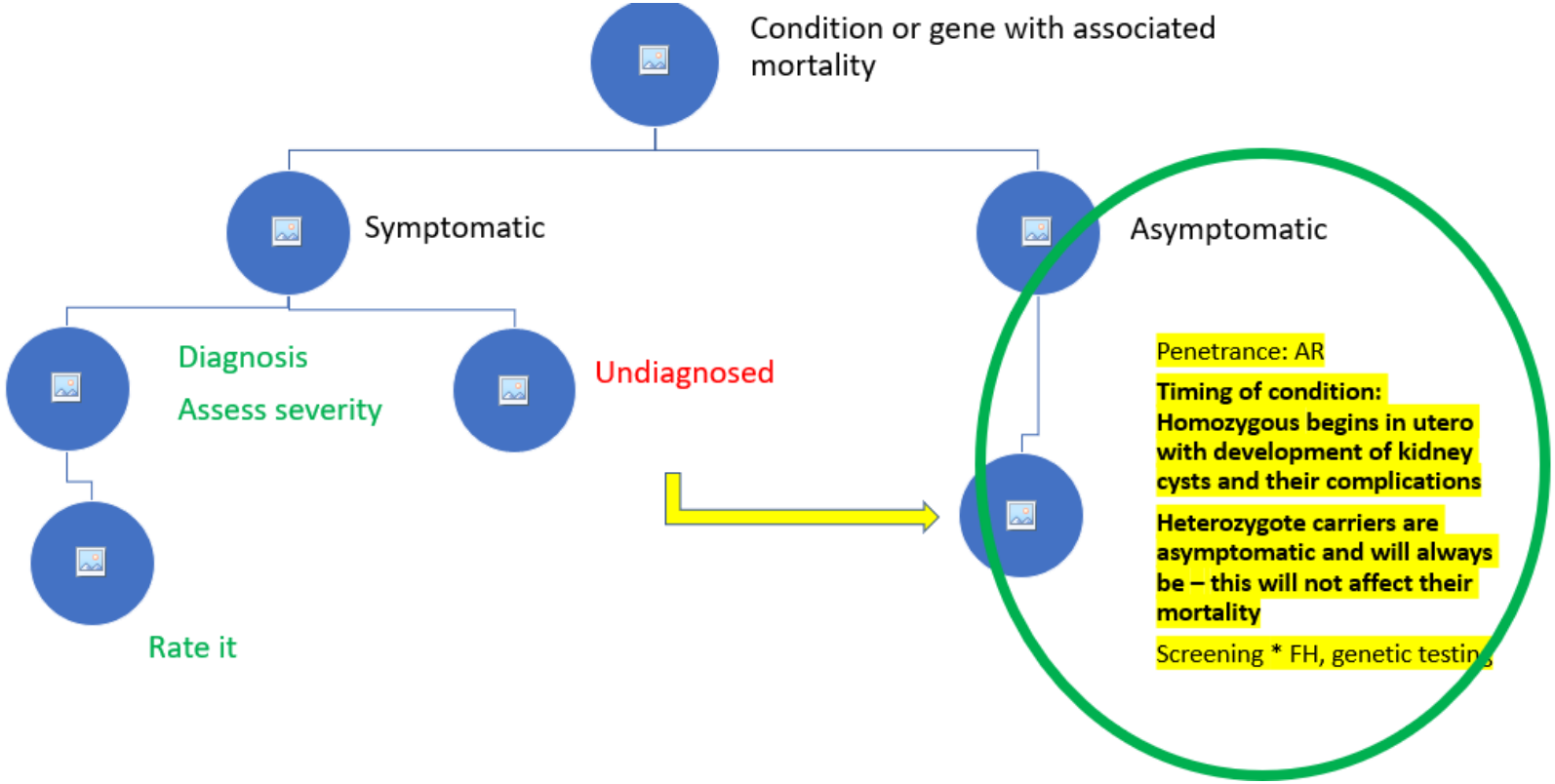
- *2-month-old child applying for $50K whose sibling died shortly after birth. Parents of this child are well and are insured with our company – policies were offered 5 years ago. After the untimely death of the sibling, the parents requested an autopsy and detailed evaluation of the cause of death. On genetic evaluation, the child was found to have autosomal recessive polycystic kidney disease.*
- *The parents were both carriers of this syndrome and therefore asymptomatic. They had been issued in the past at standard/preferred.*

1. Are we comfortable with the fact that the parents were offered?
    1. Yes
    2. No
2. Did they misrepresent?
    1. Yes
    2. No
    3. I don't know
3. Is the misrepresentation material?
    1. Yes
    2. No

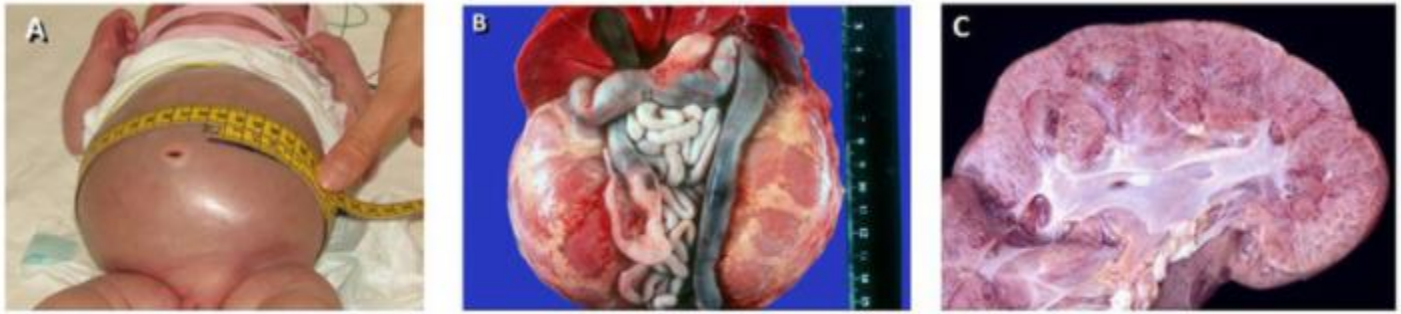
Autosomal Recessive Inheritance



Underwriting Approach – AR PKD



Autosomal Recessive PKD



www.researchgate.net/figure/Autosomal-recessive-polycystic-kidney-disease-ARPKD-A-Baby-with-distended-abdomen_fig3_323054630

Autosomal Recessive PKD

- This is an incredibly serious disease
- Death in the newborn period is between 30-50%.
- Today, with advances in medical science a fair amount of children live until 10 years of age. Renal replacement has even allowed some to live beyond.
- KEEP IN MIND – this is not ADPKD which usually manifests in a person's 40's and 50's and every affected individual has an affected parent

Autosomal Recessive PKD

- **The symptoms of autosomal recessive polycystic kidney disease (ARPKD) can vary significantly, even within the same family.**
- Onset
  - **Before birth – ultrasound**
    - they have enlarged kidneys
    - their lungs are underdeveloped
    - there's a lack of amniotic fluid surrounding the baby
  - **After birth – clinical exam**
    - significant breathing difficulties – this is caused by the lungs being underdeveloped
    - a swollen tummy (abdomen) – caused by enlargement of the kidneys
    - Potter's syndrome – where a lack of amniotic fluid leads to deformities of the limbs, face and ears; Potter's syndrome is a possibility in severe cases of ARPKD

Autosomal Recessive PKD

- **High blood pressure**
- **Liver problems (cysts, fibrosis, portal hypertension/splenomegaly) and internal bleeding**
- **Excessive urination and thirst**
- **Feeding problems**
- **Failure to thrive Faltering growth**
- **Chronic kidney disease and kidney failure**
  - Nearly all, including the milder cases, develop kidney failure by the time they're 15 to 20 years old.
  - They'll need either a kidney transplant or dialysis

Genetic Quirk #2 - continued

- *In order to ascertain the health of future children, they performed embryo harvest and did genetic assessments on the harvests*

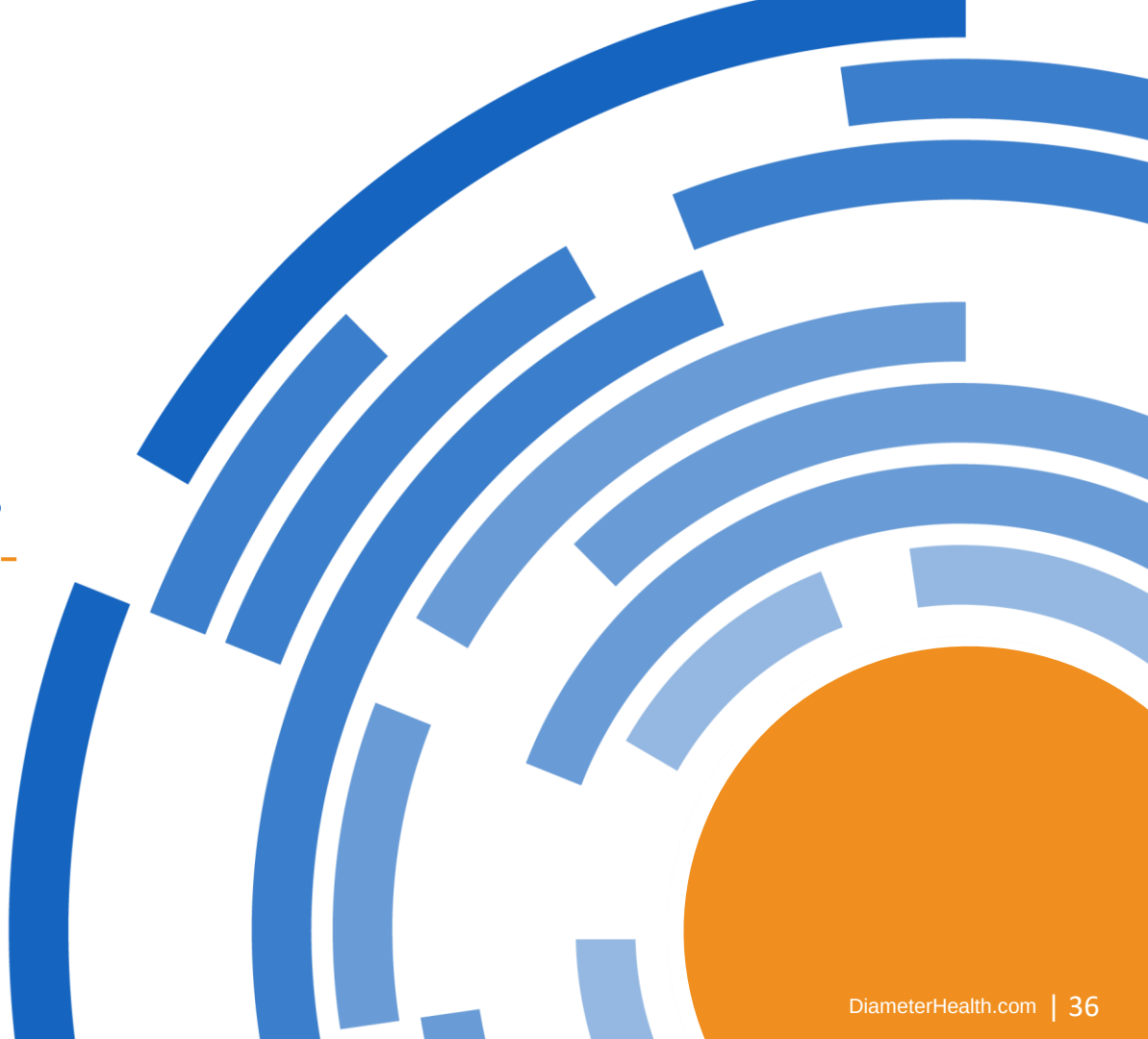
Sample ID	Polycystic kidney disease 4 PGT-M Result	Interpretation
1-CG	UNAFFECTED	NORMAL
2-CG	CARRIER *Normal maternal & mutant paternal alleles observed*	CARRIER
3-CG	UNAFFECTED	NORMAL
4-CG	UNAFFECTED	NORMAL
5-CG	Affected	Abnormal
6-CG	CARRIER *Normal maternal & mutant paternal alleles observed*	CARRIER

- *They chose embryo # 4, now the 2-month-old applicant*

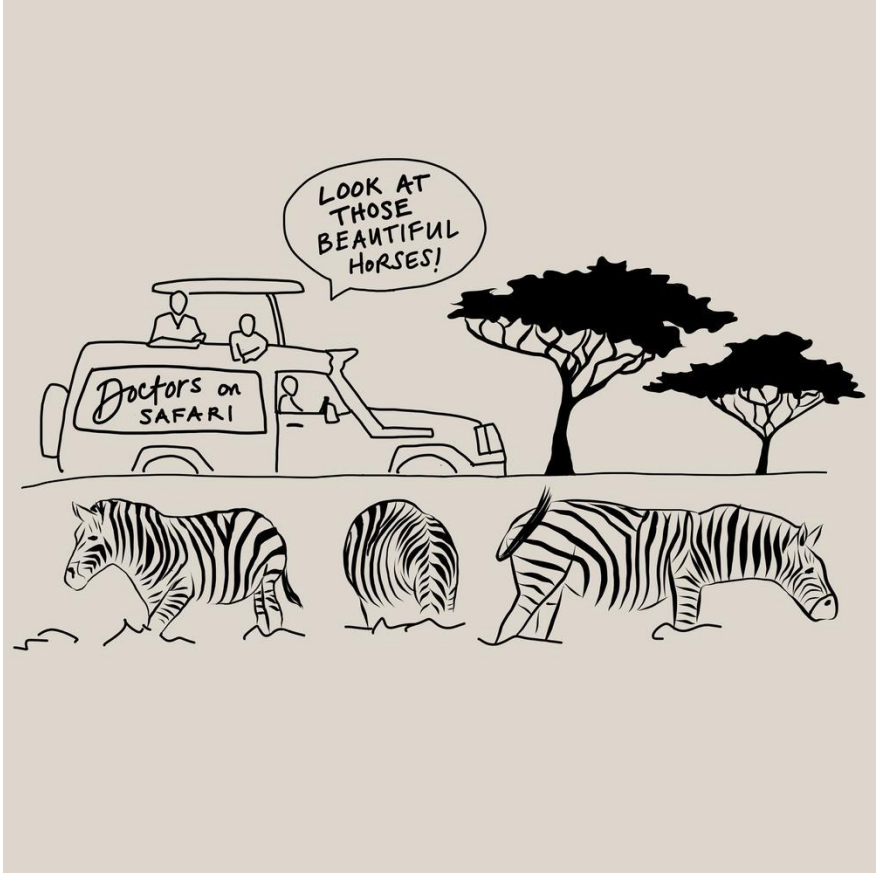
Genetic Quirk #2 - continued

- Are we comfortable taking the parents at their word that embryo # 4 is this 2-month-old applicant?
- Are we sure that cause of death of the first child was truly polycystic kidney disease?
- What are our thoughts of offering, given what we know about Florida law?
- What happens if these parents decide, in the name of solidarity for their deceased child to choose a carrier or affected embryo for a future pregnancy?
- How do we feel about the reputation risk to our company about using genetic selection as the foundation for underwriting this case?
- How does the fact that this is a $50K case factor into your decision making?

Zebras



Credit to Dr. Theodore Woodard (University of Maryland)



https://nerdwear.co/blogs/sciolist-blog/horses-not-zebras-explanation

Zebra # 1

- *18-year-old male who was diagnosed with Autism in 2015.*
- *He had formal IQ testing of 72-77.*
- *Anxiety disorder and was recommended sertraline by his psychiatrist, but he has continually refused to do so.*
- *He has obsessive compulsive traits and regularly plays video games.*
- *He is not in any formal educational or vocational program – by his choice. He has a great relationship with his mother, but regularly fights with his sister.*

Psychological diagnoses

COPE summary:

- ASD
- Borderline IQ
- severe expressive and receptive language delay
- Tourette Syndrome
- Anxiety
- Attention problems
- School avoidance

Autism

- Exists on a continuum
  - Persistent deficits in social communication and interaction
  - Repetitive patters of behavior, interests and activities
- More complex cases diagnosed in early childhood. Milder cases may not be diagnosed until adulthood
- Masking features to blend – this may cause anxiety
- Intellectual disability may exist, but not the hallmark

Prevalence

- 15-25/1000
- Males 4x greater prevalence than females
- Siblings can have 20% prevalence

- Intellectual Delay in 50%
- ADHD in 30%
- 25% as part of clinically defined syndromes
  - Tuberous Sclerosis, Fragile X, Chromosomal Duplication syndromes, Angelman syndrome, Rett Syndrome, Syndromes of Macrocephaly, CHARGE Syndrome, Joubert Syndrome, Smith-Lemli-Opitz Syndrome and Timothy Syndrome

Comorbid illness

- Seizures
- Lead poisoning
- Depression
- Anxiety
- Hyperactivity
- Sleep disturbances
- Feeding and nutritional issues
- Impairments of daily living

Severity

Severity	Social communication / Interaction	Repetitive / Restricted behavior
Level 1: Requiring support (Mild)	Noticeable impairment without support – difficulty initiating social interactions, visible social isolation	Behaviors significantly interfere with function – difficulty in switching between behaviors, focus on special interests (trains), general topics or collecting
Level 2: Requiring substantial support (Moderate)	Marked deficits in communication – reduced responses to social cues	Behaviors sufficiently frequent and obvious to casual observer – substantial rigidity in changing focus or attention
Level 3: Requiring very substantial support (Severe)	Severe impairments in functioning – nonverbal or physical gesturing to communicate, presence of echolalia	Behaviors markedly interfere with function– rocking or spinning, flapping, sniffing, handling, mouthing

Mortality

Table 3 Risk for all-cause mortality for the entire autism spectrum disorder (ASD) group, as well as separately for females and males, and low-functioning ASD and high-functioning ASD groups

	Controls Number of deaths (%)	ASD OR (95% CI) Number of deaths (%)	Low-functioning ASD OR (95% CI) Number of deaths (%)	High-functioning ASD OR (95% CI) Number of deaths (%)
Total	24 358 (0.91)	2.56 (2.38–2.76) 706 (2.60)	5.78** (4.94–6.75) 169 (2.71)	2.18 (2.00–2.38) 537 (2.57)
Females	11 693 (1.39)	2.24 (1.99–2.51) 296 (3.51)	8.52 (6.55–11.08) 61 (3.00)	1.88 (1.65–2.14) 235 (3.67)
Males	12 665 (0.69)	2.87* (2.60–3.16) 410 (2.19)	4.88 (4.02–5.93) 108 (2.57)	2.49 (2.22–2.80) 302 (2.08)

ASD, autism spectrum disorder; OR, odds ratio; CI, confidence interval.
*Partial likelihood ratio test for interaction effect ASD × gender, $P = 0.001$.
**Partial likelihood ratio test for model selection (low-functioning ASD/high-functioning ASD), $P < 0.001$.

Mortality

Table 4 Cause-specific mortality in relation to ASD and separately for low-functioning ASD and high-functioning ASD[a]

	Controls, *n* of deaths (%)	ASD OR (95% CI) *n* of deaths (%)	Low-functioning ASD OR (95% CI), *n* of deaths (%)	High-functioning ASD OR (95% CI), *n* of deaths (%)
Infections	245 (0.01)	1.83 (0.75–4.30) 5 (0.02)	N/A	N/A
Neoplasms	4493 (0.17)	1.80 (1.46–2.23) 88 (0.32)	2.12 (1.25–3.61) 14 (0.22)	1.75 (1.39–2.21) 74 (0.35)
Endocrine	474 (0.02)	3.70 (2.34–5.87) 19 (0.07)	8.89 (3.52–22.41) 5 (0.08)	3.07 (1.80–5.23) 14 (0.07)
Mental and behavioural disorders	925 (0.03)	2.80 (1.94–4.03) 30 (0.11)	21.81** (12.20–39.00) 14 (0.22)	1.58 (0.96–2.59) 16 (0.08)
Nervous system	737 (0.03)	7.49 (5.78–9.72) 62 (0.23)	40.56** (26.82–61.33) 32 (0.51)	3.98 (2.76–5.74) 30 (0.14)
Circulatory system	8820 (0.33)	1.49 (1.27–1.75) 157 (0.58)	4.61** (3.06–6.95) 24 (0.38)	1.33 (1.12–1.58) 133 (0.64)
Respiratory system	1351 (0.05)	2.68 (1.99–3.62) 45 (0.17)	13.92** (7.04–27.50) 10 (0.16)	2.17 (1.55–3.05) 35 (0.17)
Digestive system	733 (0.03)	3.31 (2.25–4.87) 27 (0.10)	9.13* (4.42–18.87) 8 (0.13)	2.61 (1.65–4.12) 19 (0.09)
Genitourinary system	253 (0.01)	3.82 (2.13–6.84) 12 (0.04)	N/A	N/A
Congenital malformations	106 (<0.01)	19.10 (11.94–30.55) 21 (0.08)	38.75* (20.39–73.64) 13 (0.21)	10.38 (4.98–21.61) 8 (0.04)
Symptoms, signs and abnormal findings, other	618 (0.02)	1.81 (1.06–3.08) 14 (0.05)	N/A	N/A
Suicide	1094 (0.04)	7.55 (6.04–9.44) 83 (0.31)	2.41 (1.14–5.11) 7 (0.11)	9.40** (7.43–11.90) 76 (0.36)
External causes, other	1696 (0.06)	1.67 (1.16–2.40) 30 (0.11)	1.53 (0.69–3.44) 6 (0.10)	1.71 (1.14–2.56) 24 (0.11)
Other	232 (0.01)	5.84 (3.46–9.86) 15 (0.06)	N/A	N/A

ASD, autism spectrum disorder; OR, odds ratio; CI, confidence interval.
a. Missing data on primary cause of death ($n = 2677$, <0.5% in both groups) are not included in the analyses; N/A analyses were not performed owing to the low number of cases in certain cells; partial likelihood ratio test for model selection (low-functioning ASD/high-functioning ASD).
*$P < 0.01$ (Digestive $P = 0.009$; Congenital malformations $P = 0.007$); **$P < 0.001$.

Diameter Health

Mortality Notes

- Adaptive social and communication strategies can improve mortality
- Suicide presents the greatest cause of mortality for high-functioning autistic patients
  - In both those with and without documented psychiatric illness
  - Social disengagement and greater insight; access
- Diseases are diagnosed late and in advanced presentation

Zebra # 1

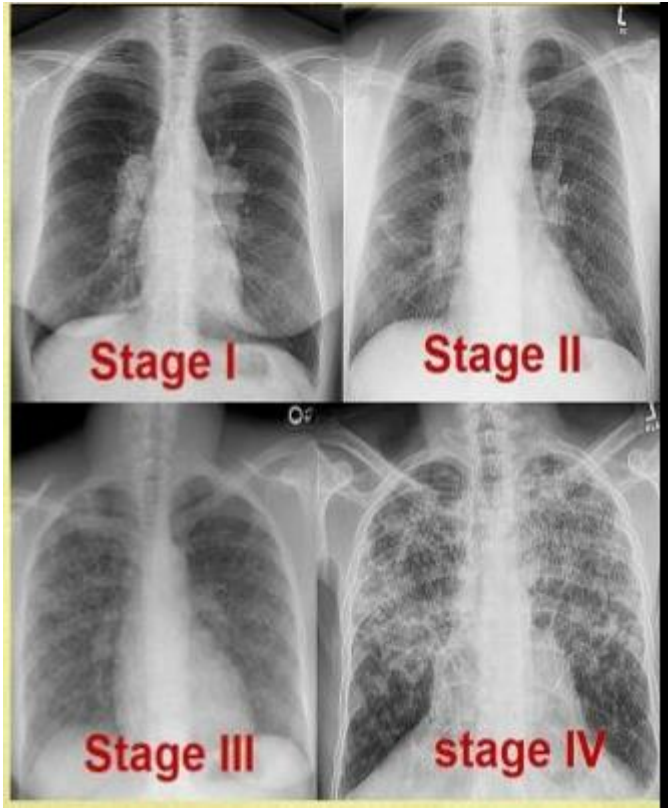
- *18-year-old male who was diagnosed with Autism in 2015.*
- *He had formal IQ testing of 72-77.*
- *Anxiety disorder and was recommended sertraline by his psychiatrist, but he has continually refused to do so.*
- *He has obsessive compulsive traits and regularly plays video games.*
- *He is not in any formal educational or vocational program – by his choice. He has a great relationship with his mother, but regularly fights with his sister.*

- Do we offer? What's worrisome?
- Can we ever offer?
- What would we need for an offer?

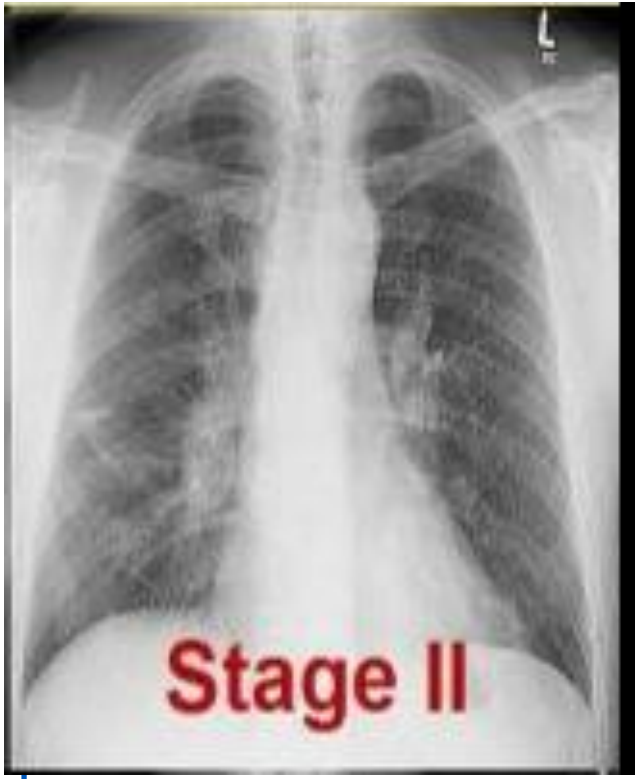
Zebra #2

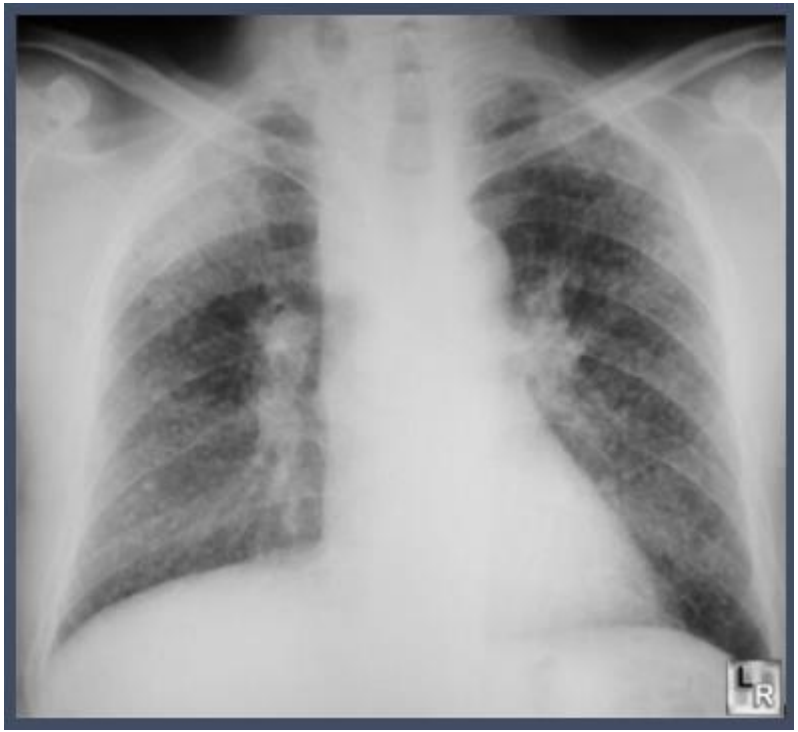
- *Male 19 years, applying for 500k*
- *occupation: miner*
- *Last followed in 9/2019*
- *hx stage 2 sarcoidosis diagnosed in 2017 - self-resolution without prednisone*
- *has always had hemoptysis*
- *PFT's performed by his primary in 8/2019*
- *CT chest 9/2019*
  - *appearance of micronodular involvement in the upper lobes/pulmonary involvement 2ndary to sarcoidosis (dx in 2017) the rest seems stable*
- *Never saw a pulmonologist*
- *Due to micronodules in the upper lobes and hemoptysis present Std? or better to apply small rating*
-
- *your opinion please, thank you*

Sarcoid



Silicosis

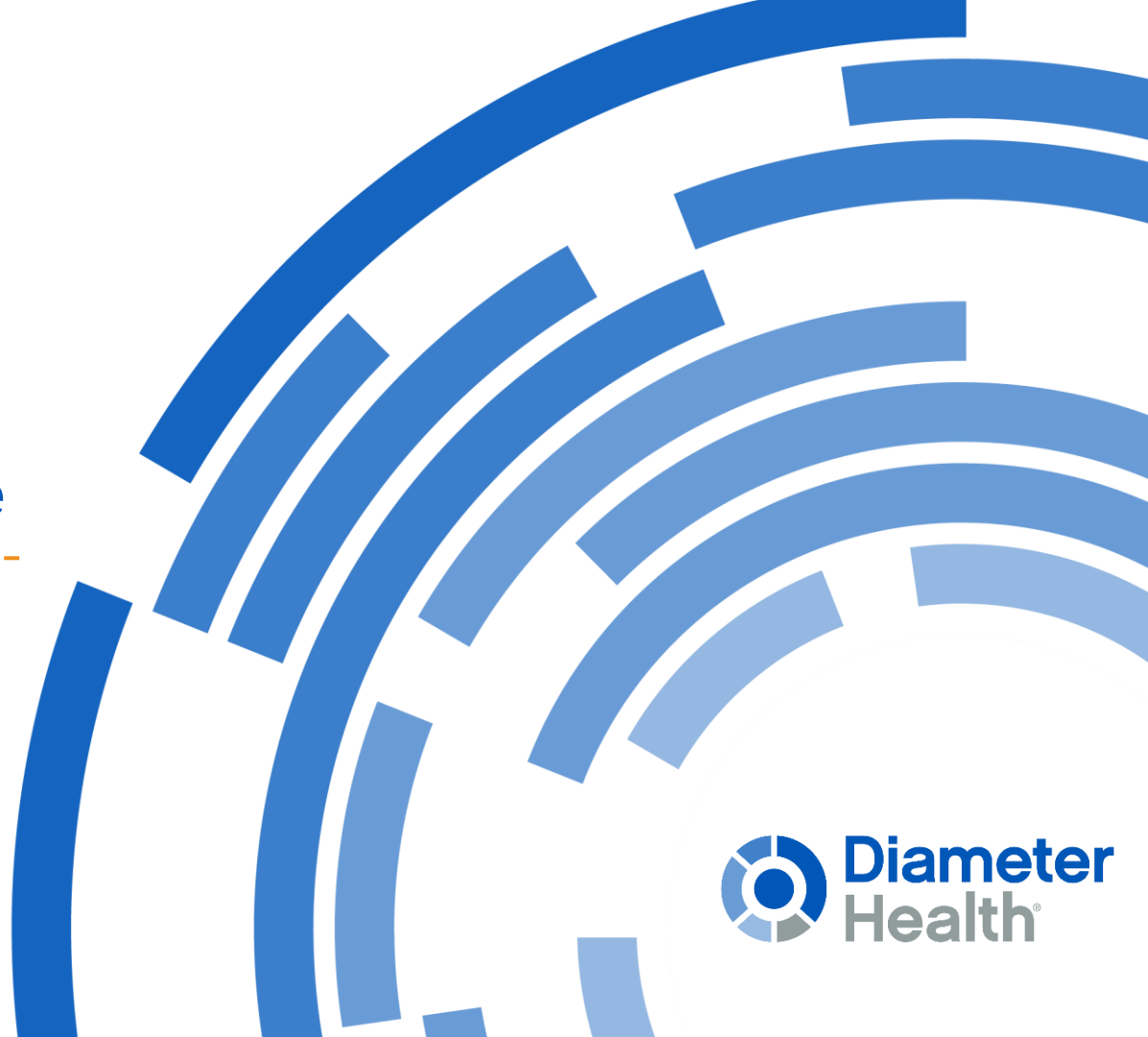




Zebra #2

- Can we offer?
- What do we need in order to consider?
- Are we worried he has not seen a pulmonologist?
- Are we worried he has not been seen since 2019?

If Time Case



Genetic Quirk #3

- *Male Non-smoker Aged 50*
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- *no adverse med hx declared*
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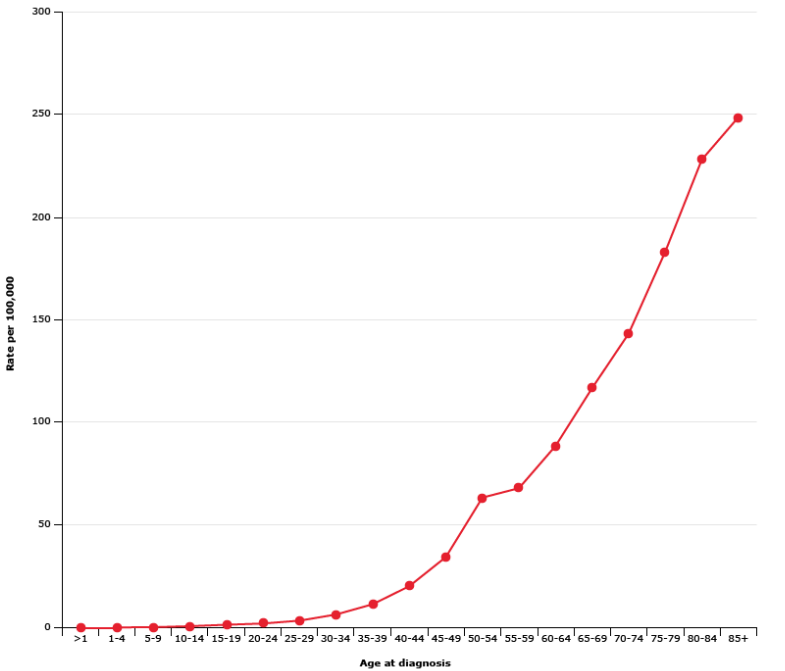
- *insured had a colonoscopy in mar 2014 normal*
- *likely due for f/u colon screening ->> PP or could we consider now for small substandard rating*

Colon cancer risk

Increasing incidence of colorectal cancer in the United States with age, SEER 2014 to 2018



The age-specific incidence of colorectal cancer was measured between 2014 and 2018 in men and women of all races.

SEER: Surveillance, Epidemiology, and End Results.

Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2014-2018. Available at: https://seer.cancer.gov/explorer/application.html?site=20&data_type=1&graph_type=3&compareBy=sex&chk_sex_1=1&rate_type=2&race=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2 (Accessed on July 13, 2021).

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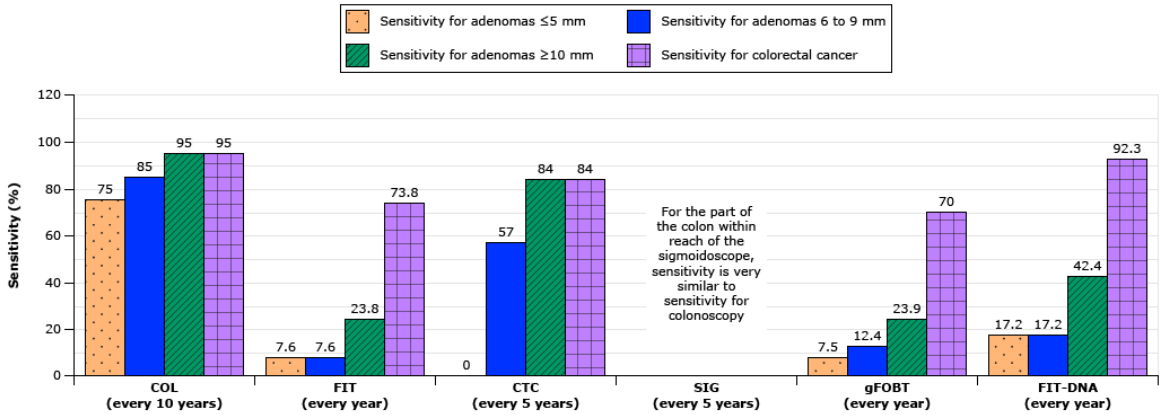
Screening strategies for colon cancer

- A shift to age 45
  - The USPSTF - 45 (Grade B) - strongest recommendation (Grade A) for initiating at age 50
  - The American College of Gastroenterology (ACG) – 45
  - Initiating screening at age 45 years is a “qualified” recommendation from the American Cancer Society (ACS)
  - Initiating screening at age 50 years for average-risk adults is recommended by the Canadian Task Force on Preventive Health Care (CTFPHC), the European Council, the American Academy of Family Physicians (AAFP), and the American College of Physicians (ACP)
- We continue to screen for CRC through age 75 years for average-risk patients, as long as their life expectancy is 10 years or greater.

Testing in CRC

Estimated sensitivity, specificity, and cancer-specific deaths averted for each colorectal cancer screening strategy



Test specificity	86	96.4	88	87	92.5	89.8
Colorectal cancer deaths averted per 1000 40-year-olds (n)*	22 to 24	20 to 23	16 to 24	16 to 21	20 to 23	21 to 24

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

COL: colonoscopy; FIT: fecal immunochemical test; CTC: computed tomography colonography; SIG: sigmoidoscopy; gFOBT: guaiac-based fecal occult blood test; FIT-DNA: multitargeted stool DNA test.

* Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance. Ranges reflect results from 3 models.

Data from:

1. *Zauber A, Knudsen A, Rutter CM, et al. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. AHRQ Publication No. 14-05203-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; October 2015.*
2. *Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016; 315:2595.*

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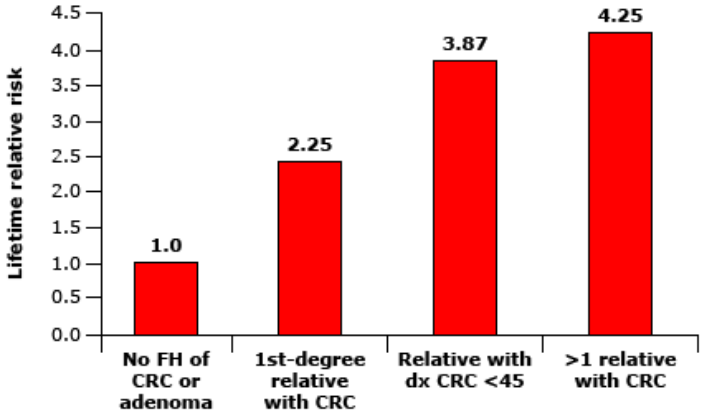
What tests to use?

- Colonoscopy every 10 years for most patients at average risk for CRC who are willing to undergo this procedure.
  - If unable or unwilling
  - FIT for occult blood annually on a single sample, by multitarget stool DNA (MT-sDNA) testing every three years
  - Computed tomography colonography (CTC) every five years
- Other tests - sigmoidoscopy with FIT or with FOBT, sigmoidoscopy alone, FOBT alone, and capsule colonoscopy.
- Colorectal screening should **not** be based on the result of a single office-based FOBT performed following a digital rectal examination (DRE)
- Barium enemas are no longer recommended

What about family history?

Risk of colon cancer associated with a family history



The highest risk is in people with multiple first-degree relatives or relatives who have developed CRC at a relatively young age.

FH: family history; CRC: colorectal cancer; dx: diagnosis.

Data from: Johns LE, Houlston RS. Am J Gastroenterol 2001; 96:2992.

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Diameter Health

Colon Cancer Syndromes

TABLE 1

Summary of Conditions That Increase the Risk of Colorectal Cancer

Condition	Definition	Prevalence	Average age at symptomatic presentation	Average age at diagnosis	When to start screening	Screening interval	Recommending organizations	Comments
Attenuated familial adenomatous polyposis[4,5]	10 to 99 synchronous advanced adenomas	Unknown	52 years	58 years (range = 29 to 81 years); 69% of patients studied developed CRC by 80 years of age	Late teens to mid-20s	Colonoscopy every one to two years	ACG, NCCN	Proximal colonic distribution necessitates colonoscopy for all screening
Familial adenomatous polyposis[4,6,7]	≥ 100 colorectal adenomas	Approximately three cases per 100,000	36 years (range = 4 to 72 years)	39 years; risk of developing CRC by 45 years of age is 87%	Sigmoidoscopy starting at 10 to 12 years of age	Sigmoidoscopy every one to two years until polyp is found, then colonoscopy	ACG, NCCN	If colectomy is delayed more than one year after polyps are found, colonoscopy should be performed annually
Hereditary nonpolyposis colorectal cancer[4,8,9]	May be defined clinically or by presence of one of five DNA mismatch repair genes	Unknown but estimated to be one in 440	< 45 years	45 years; lifetime risk of CRC is 75% to 80%	25 years of age or five years earlier than the first cancer case in the family, whichever comes first	Colonoscopy every one to two years	International Collaborative Group on HNPCC; Revised Bethesda Guidelines for HNPCC (National Cancer Institute); European Hereditary Tumour Group	Simplified clinical screening criteria: Patients with a first-degree relative with CRC diagnosed before 50 years of age Presence of synchronous and/or metachronous CRC or other HNPCC-associated tumors (e.g., endometrial or gastric)
Inflammatory bowel disease[10–13]	Ulcerative colitis or Crohn disease with colonic involvement	Crohn disease: 11 per 100,000 Ulcerative colitis: 12 per 100,000	Crohn disease: 30 years Ulcerative colitis: 35 years	40 to 50 years; 4% to 5% lifetime risk of CRC	Colonoscopy eight to 10 years after the onset of symptoms	Every one to three years	Crohn's & Colitis Foundation; American Cancer Society Colorectal Cancer Advisory group	Annual surveillance colonoscopy in patients with primary sclerosing cholangitis
MUTYH-associated polyposis[4,6,9,14]	Typically < 100 colorectal adenomas	Less than one in 10,000	Unknown	48 years; risk of CRC is 19% by 50 years of age and 43% by 60 years of age	Colonoscopy beginning in late teens to mid-20s	One to two years	ACG, NCCN	First described in 2002
Peutz-Jeghers syndrome[4,6]	Hamartomatous polyposis	One in 50,000 to 200,000	Polyp growth begins in the first decade of life, but patients typically do not develop symptoms until the second or third decade	Unknown	Esophagogastroduodenoscopy, colonoscopy, and video capsule endoscopy should begin at eight years of age and, if negative, be repeated every three years	If polyps, colonoscopy every three years If no polyps, wait until 18 years of age, then colonoscopy every three years; repeat video capsule endoscopy every three years	ACG, NCCN	Intussusception is a common complication typically occurring in individuals younger than 20 years
Sessile serrated adenomatous polyposis[15,16]	At least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis More than 20 serrated polyps of any size distributed throughout the colon	Unknown but estimated to be one in 2,000 to 3,000	44 to 62 years	44 to 62 years; 25% to 70% have CRC at the time of diagnosis	Colonoscopy in first-degree relatives of patients with sessile serrated adenomatous polyposis syndrome beginning at 40 years of age or 10 years younger than the age at diagnosis of the youngest affected relative	Annual colonoscopy with intent to clear proximal colon of all serrated lesions Colonoscopy every five years in first-degree relatives	ACG	Surgery is indicated when CRC is diagnosed or polyps cannot be controlled endoscopically Following resection, endoscopic surveillance of any residual colon and rectum should be performed every six to 12 months

ACG = American College of Gastroenterology; CRC = colorectal cancer; HNPCC = hereditary nonpolyposis colorectal cancer; NCCN = National Comprehensive Cancer Network.

Information from references 4 through 16.

www.aafp.org/afp/2018/0115/hi-res/afp20180115p111-t2.gif

Family history screening

TABLE 2

Screening Guidelines for Individuals with a Family History of Advanced Adenomas or Colorectal Cancer

Family history*	Risk of CRC (vs. general population)	Recommendations
One first-degree relative with CRC or advanced adenoma diagnosed before 60 years of age, or two first-degree relatives diagnosed at any age	Three- to fourfold	Start screening colonoscopy at 40 years of age or 10 years younger than the earliest diagnosis in the patient's family, whichever comes first; colonoscopy should be repeated every five years
One first-degree relative with CRC or advanced adenoma diagnosed at 60 years or older, or two second-degree relatives with CRC	Two- to threefold	Start screening colonoscopy at 40 years of age; colonoscopy should be repeated every 10 years
One second- or third-degree relative with CRC	1.5-fold	Average-risk screening (e.g., start at 50 years of age)

CRC = colorectal cancer.

*—First-degree relatives include parents, siblings, and children. Second-degree relatives include grandparents, aunts, and uncles. Third-degree relatives include great-grandparents and cousins.

Information from references 3, 5, and 20.

www.aafp.org/afp/2018/0115/hi-res/afp20180115p111-t2.gif

Genetic Quirk #3 - Poll Question

- *Male Non-smoker Aged 50*
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- *likely due for f/u colon screening ->> PP or could we consider now for small substandard rating*

1. Offer now?
2. What would you need to offer?
3. Would you offer standard?
    1. Yes
    2. No
4. Preferred?
    1. Yes
    2. No
5. How would you handle polyps on cancer screening?
6. What about the law of large numbers?

Questions