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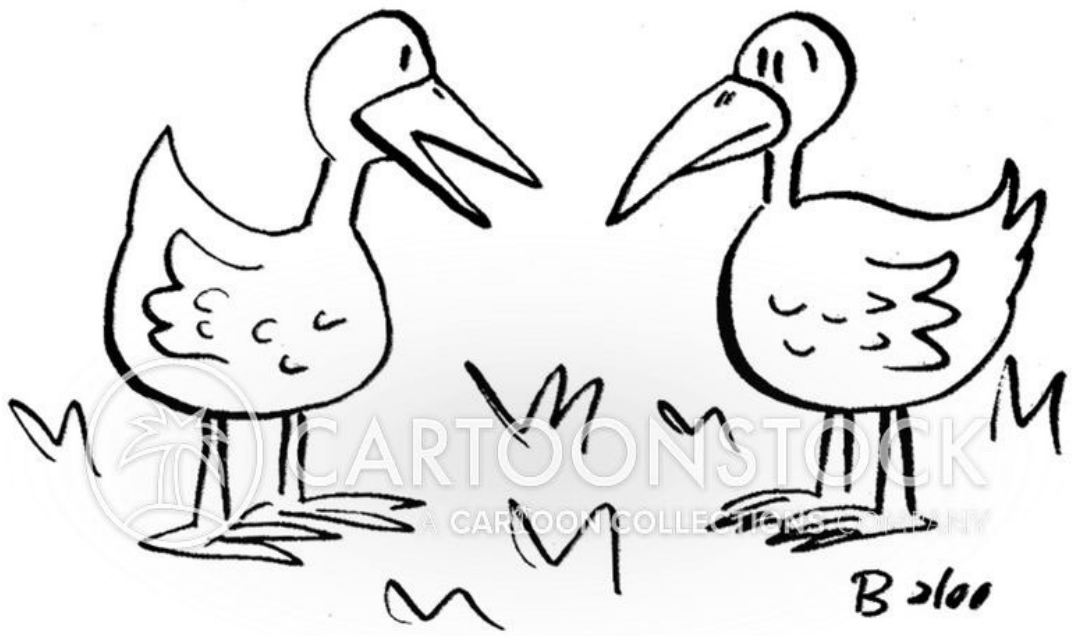

"I got up at 5:30 once and caught a worm — it wasn't worth it, believe me."

The early bird ate too many worms and died

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COMMON GENETIC DISORDERS FOR THAI INTERNISTS

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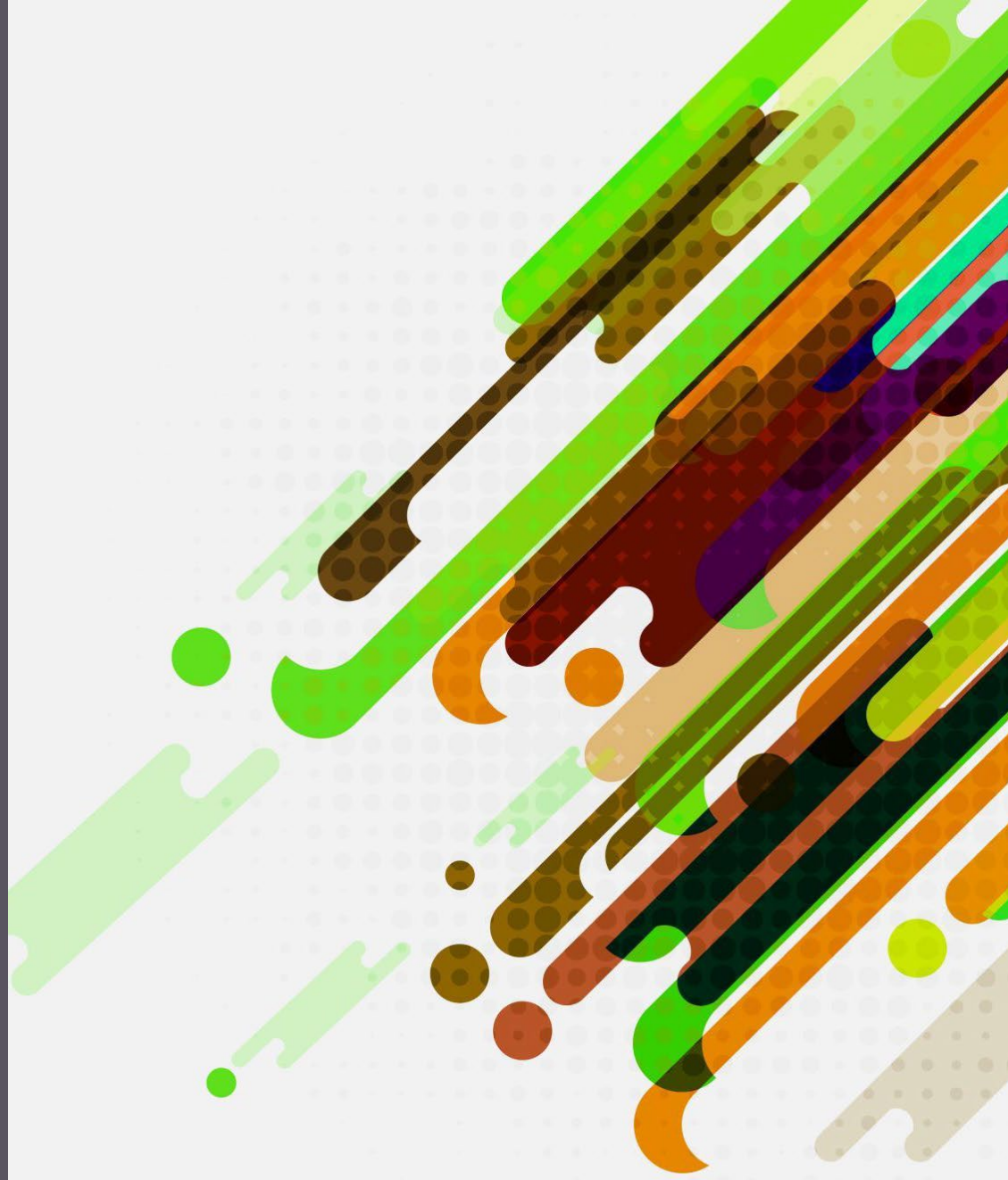


Disclosure

Medical Genetics Consultant: KCMH, Rama Hosp, BH, BNH, MPKH, PYT1 Hosp

Laboratory Genetics Consultant: Grace Sciences, Genforch, Precision Health, Excellence Center for Genomics and Precision Medicine (KCMH)

Honorarium and Travel Grant: Takeda, Roche, Sanofi, Pfizer

Member of Thai Society of Human Genetics and Thai Association of Medical Genetics and Genomics

Common Genetic Disorders for Thai Internists

Genetic Diseases Classification

Prevalence of Genetic Diseases

Adult-onset genetic diseases

Top Five Genetic Diseases That Thai Internists Must Know

- *Glucose-6-Phosphate Dehydrogenase Deficiency (X-linked)*
- *Familial Hypercholesterolemia (Autosomal Dominant)*
- *Hypertrophic Cardiomyopathy (Autosomal Dominant)*
- *Thalassemia and Hemoglobinopathies (Autosomal Recessive)*
- *Hereditary Breast-Ovarian Cancer Syndrome (Autosomal Dominant)*

Genetic Disorders Classification

1. Monogenic (Mendelian, Mitochondrial, Imprinting)
2. Microdeletion/Microduplication and Chromosomal Rearrangement Disorders (Contiguous Genes Syndrome, Genomic Disorders)
3. Chromosomal Disorders (Aneuploidy, Polyploidy – mosaicism, segmental)
4. Multifactorial Disorders (Complex Inheritance)

Prevalence of Genetic Diseases

1. Monogenic Disorders:	1/300
2. Genomics Disorders:	1/200
3. Chromosomal Disorders	1/500
4. Complex Inheritance Disorders	1/20

6% of population

Estimation of Rare Diseases Prevalence

Rare diseases affect about 300 million people globally

80% of rare diseases are genetic disorders

Genetic diseases with known causative genes are more than 6,000 disorders


TOP 15

HEREDITARY BREAST-OVARIAN CANCER SYNDROME

Hereditary Breast-Ovarian Cancer Syndrome

- **Most commonly caused by the pathogenic/likely pathogenic variants in *BRCA1* or *BRCA2* genes.**

- **When to suspect: A SPecial FROG**
  - **A** Age **< 40 years old**
  - **S Site: bilateral or multifocal**
  - **P Pathology: Triple Negative -> *BRCA1***
  - **F Family history**
  - **R Race: Ashkenazi Jewish Ancestry**
  - **O Other Cancers: high grade serous ovarian cancers, prostate cancer, pancreatic cancer, melanoma**
  - **G Gender: male breast cancer**

Molecular Genetic Testing

Gene [1]	Proportion of *BRCA1*- & *BRCA2*-Associated HBOC Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
BRCA1	66%	87%-89% [5]	11%-13% [5]
BRCA2	34%	97%-98% [5]	2%-3% [5]

Differential Diagnosis

High-penetrance (high-risk) genes for breast cancer			
CDH1	Hereditary diffuse gastric cancer	AD	Breast cancer (lobular), diffuse gastric cancer. Majority of cancers occur before age 40 yrs.
PALB2	*PALB2*-related cancer susceptibility (OMIM 610355)	AD	Breast cancer ≤58%, [1] ovarian cancer, male breast cancer, pancreatic cancer
PTEN	*PTEN* hamartoma tumor syndrome	AD	Breast cancer. Other cancers: thyroid, renal cell carcinoma, endometrial, colorectal. Multiple hamartomas, macrocephaly, trichilemmomas, papillomatous papules. Affected persons usually present by late 20s.
STK11	Peutz-Jeghers syndrome	AD	Breast cancer. Other cancers: GI, ovarian (mostly SCTAT), cervical (adenoma malignum), pancreatic, Sertoli cell testicular. GI polyposis, mucocutaneous pigmentation, hyperpigmented macules on fingers.
TP53	Li-Fraumeni syndrome	AD	Breast cancer (often premenopausal). Other cancers: soft tissue sarcoma, osteosarcoma, brain, adrenocortical carcinoma, leukemias. Early-onset & multiple primary cancers.

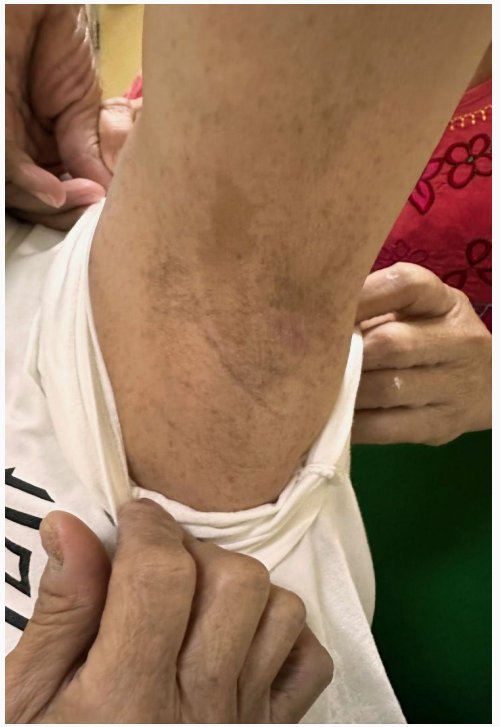
Differential Diagnosis

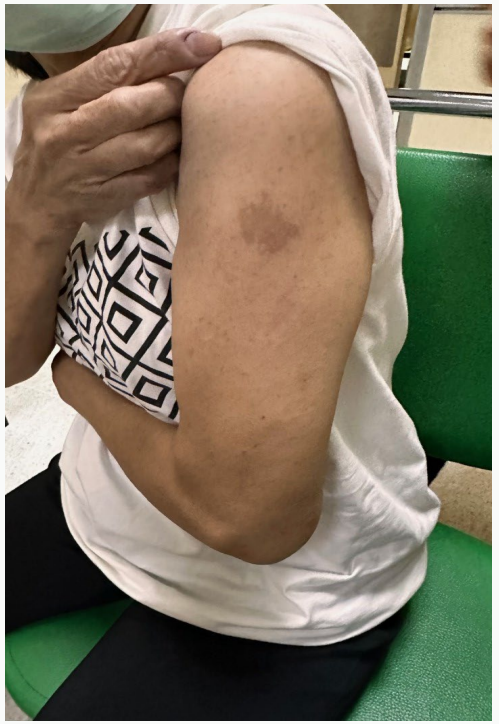
Moderate-penetrance (moderate-risk) genes for breast &/or ovarian cancer			
ATM	*ATM*-related cancer susceptibility (*ATM* heterozygotes; see Ataxia-Telangiectasia.)	AD	Breast cancer
BARD1	*BARD1*-related cancer susceptibility (OMIM 114480)	AD	Breast cancer
BRIP1	*BRIP1*-related cancer susceptibility (OMIM 605882)	AD	Epithelial ovarian cancer, [2] possible ↑ risk for breast cancer
CHEK2	*CHEK2*-related cancer susceptibility (OMIM 604373)	AD	Breast cancer [3]

Differential Diagnosis

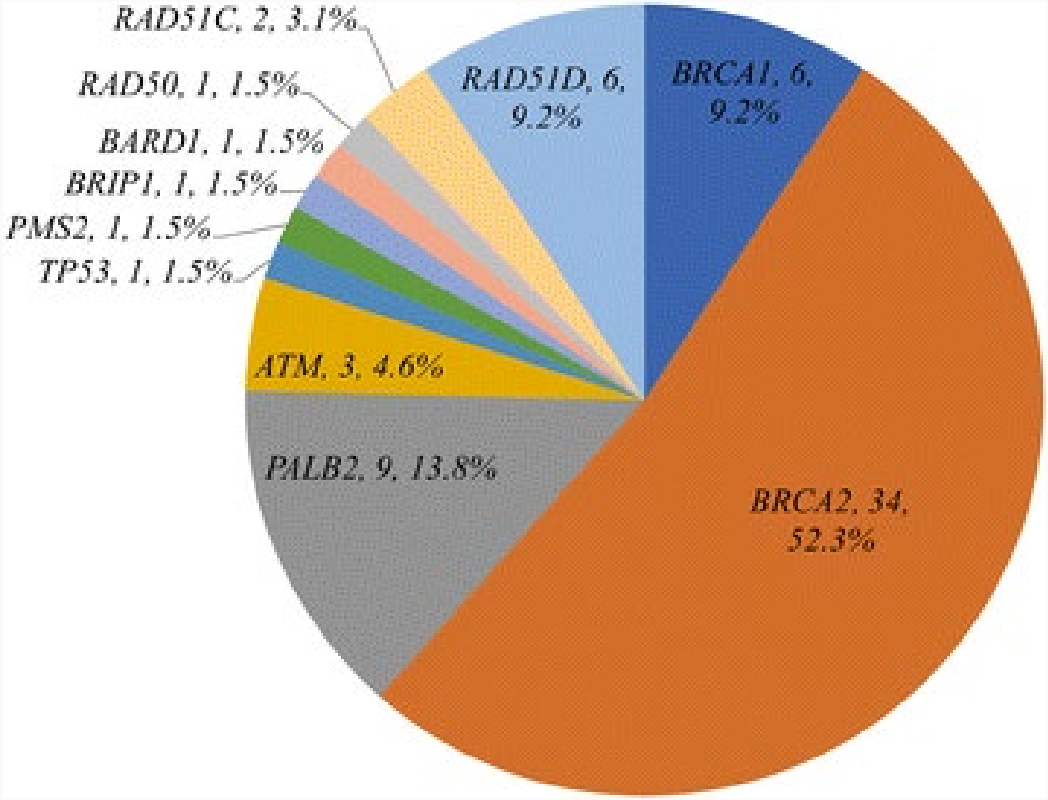
	NF1 women		Finnish women
Age group	Risk (%)	95% CI	Risk (%)
20–29	0.55	0.00–1.62	0.03
30–39	4.74	1.48–7.89	0.34
40–49	3.92	0.77–6.96	1.50
50–59[a]	5.89	1.86–9.76	2.64
60–69[a]	4.18	0.09–8.11	2.88
70–79	3.99	0.00–9.26	2.44

Abbreviations: CI = confidence interval; NF1 = neurofibromatosis 1.
[a]Women aged 50–69 years are routinely invited to mammography screening in Finland.





Distribution of Susceptibility Genes



Testing Strategies

- **Targeted Testing: Ashkenazi Jewish >99%**
  - *BRCA1* c.68_69delAG (BIC: 185delAG)
  - *BRCA1* c.5266dupC (BIC: 5382insC), and
  - *BRCA2* c.5946delT (BIC: 6174delT)

  - No hotspot mutations in Thai or other populations at this degree

Testing Strategies

***BRCA1/BRCA2* Panel**		
Deletion/Duplication Analysis – lowest available	**100 USD**	
Multi Gene Panel		
Deletion/ Duplication Analysis	**300 USD**	
Exome Sequencing Research Only – Commercially available at 250 USD		**1**
Genome Sequencing Research Only – Commercially available at?		

Risk of Cancer

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	*BRCA2*
Breast	12%	55%-72% by age 70	45%-69%
Contralateral breast cancer	2% w/in 5 yrs	20%-30% w/in 10 yrs; 40%-50% w/in 20 yrs	
Ovarian	1%-2%	39%-44%	11%-17%
Male breast	0.1%	1%-2%	6%-8%
Prostate	6% by age 69 yrs	21% by age 75 yrs; 29% by age 85 yrs	27% by age 75 yrs; 60% by age 85 yrs
Pancreatic	0.5%	1%-3%	3%-5% by age 70 yrs
Melanoma (cutaneous & ocular)	1.6%		Elevated risk

Prevalence

Estimated to be 1/500 of general population

Estimated to be 1/10 of breast cancer patient

Estimated to be 1/3 of having known risk for genetic predispose

Management

System/Concern	Evaluation	Frequency
Breast cancer	Breast self-exam	Monthly
	Clinical breast exam	Every 6-12 mos beginning at age 25 yrs
	Mammogram	Annually beginning at age 30 yrs
	Breast MRI	Annually beginning at age 25 yrs or earlier if breast cancer was diagnosed in family member < age 30 yrs
Ovarian cancer	Screening not recommended [1]	
Melanoma	Skin exam w/dermatologist	Individualized based on family history
Pancreatic cancer	In asymptomatic persons who meet criteria based on mutation status & family history, contrast-enhanced MRI/MRCP &/or EUS may be considered in a research setting to better delineate the risks & benefits of pancreatic cancer screening.	

Management

Consider prophylactic mastectomy: does not decrease all cause mortality, but decrease breast cancer incidence by 90%

Recommend prophylactic bilateral salpingo-oophorectomy at 35 years old -> monthly operation at KCMH -> will become the most common cause of surgical menopause, decrease all cause mortality

Management

- **Breast Cancer**
- **Recommend bilateral mastectomy**
- **PARP inhibitor**
    - **Early, high risk , HER2 negative BRCA1 or BRCA2 breast cancer as adjuvant therapy**
    - **Locally advanced metastatic BRCA1 or BRCA2 as single therapy**
- **Ovarian Cancer**
- **PARP inhibitor** for maintenance therapy in advanced ovarian/fallopian tube/primary peritoneal cancer

Lynch syndrome

Hereditary Non Polyposis Colorectal Cancer Syndrome (HNPCC)

Amsterdam’s criteria

Bethesda criteria

PREMM(126) Score

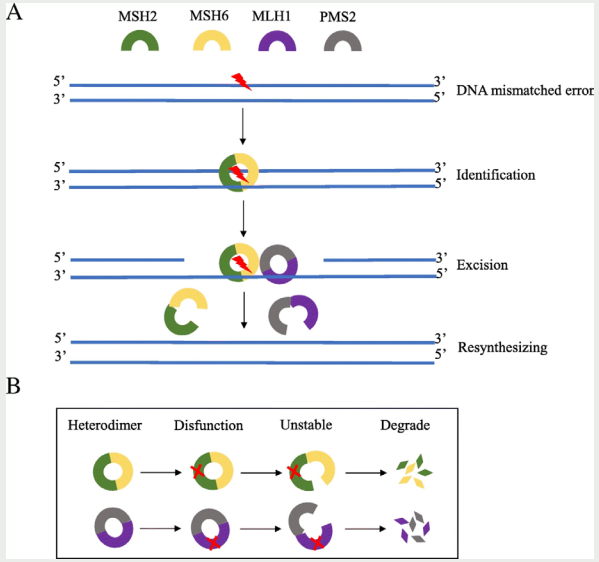
Most common cause of hereditary colon cancer: 3% of all colon cancer

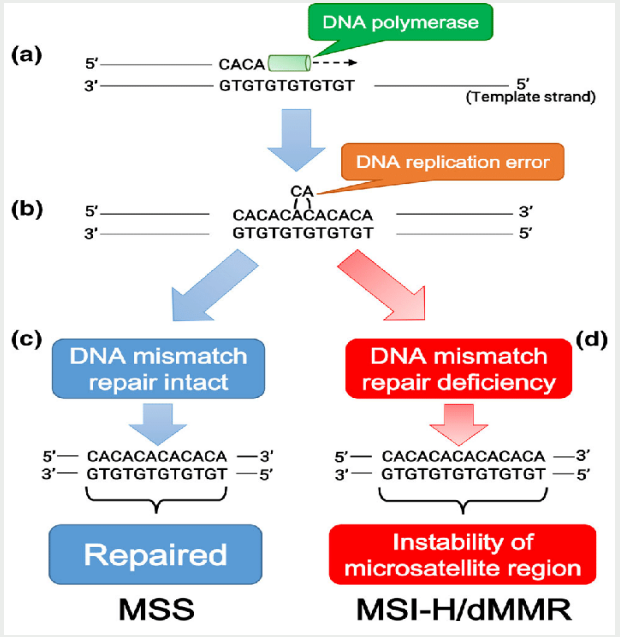
Hallmark: microsatellite Instability

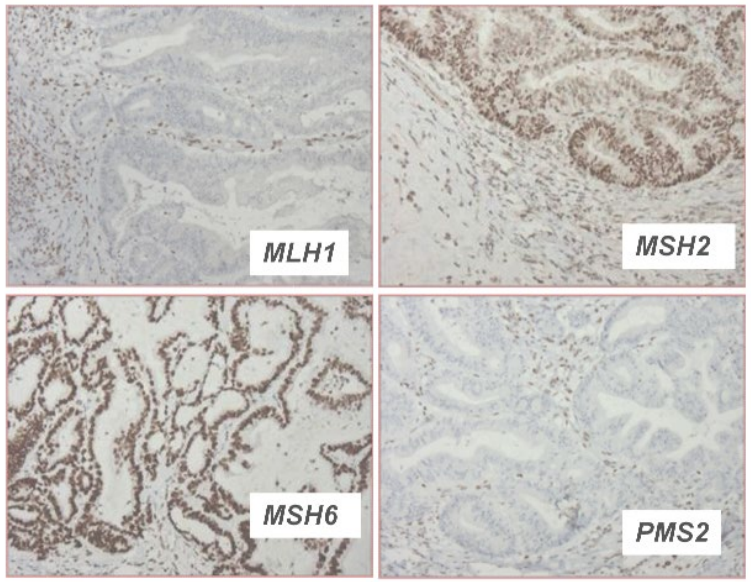
Mismatch repair genes: MLH1, PMS2, MSH2, MSH6

Life Time Risk of colon cancer: 70%

Other lynch associated cancers: endometrial cancer, stomach cancer, ovarian cancer, sebaceous carcinomas, keratoacanthomas







The Clinical Spectrum of EPCAM Mutations

2 wild type EPCAM alleles	EPCAM__MSH2 EPCAM__MSH2	=	Normal Phenotype
One wild type EPCAM allele, one with a partial deletion	EPCAM__MSH2 EPCAMSH2	=	Lynch Syndrome
One wild type EPCAM allele, one with a point mutation	EPCAM__MSH2 EPDAM__MSH2	=	Unaffected carrier, congenital tufting enteropathy
Two EPCAM alleles with point mutations	EPDAM__MSH2 EPDAM__MSH2	=	Infant affected with congenital tufting embryopathy

Differential diagnoses for Lynch syndrome include:

Attenuated familial adenomatous polyposis (APC)

MUTYH-associated polyposis syndrome (MUTYH)

Cowden disease (PTEN)

Cronkite-Canada syndrome

Familial adenomatous polyposis (APC)

Familial clustering of late-onset colorectal neoplasms

Hyperplastic polyps

Juvenile polyposis syndrome (BMPR1A, SMAD4)

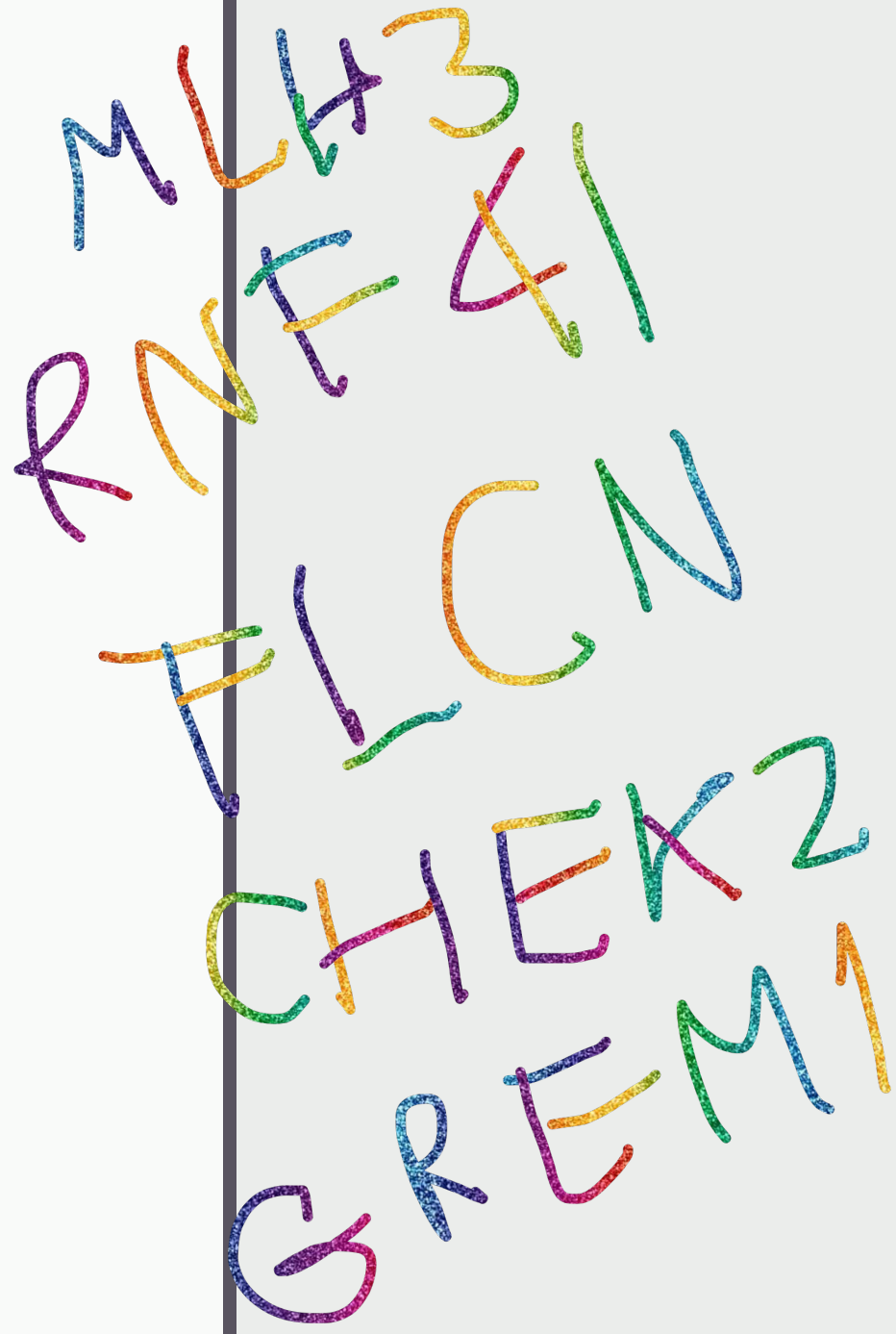
Lymphomatous polyposis

Muir-Torre syndrome

Nodular lymphoid hyperplasia

POLE, POLD1 polymerase proofreading associated polyposis

PeutJjegher syndrome (STK11)



Cancer risks by gene by 70 years

	G.	1.	2.	6.	P2.	EP
Colorectum.	2.	50.	45.	25.	3.	75.
Endometrium.	1.	35.	46.	41.	13.	12
Ovary.		1.	11.	17.	11.	3
Stomach.		1.	12.	13.	7.	
Prostate.		4.	7.	16.	5.	5
Ureter/Kidney.	1.		3.	14.	3.	4

Lynch syndrome Screening and management

Colonoscopy begin 25 or 5 yrs before earliest every 1-2 years

Endometrial biopsy begin 35 yrs every 1-2 years

Stomach begin 40 yrs (with FH or Asian)

Pancreatic begin 50 yrs (with FH): ?,?

Urinary tract begin 30 yrs (with FH)

Ovary ?????????????

Lynch syndrome

Prevalence 1/279

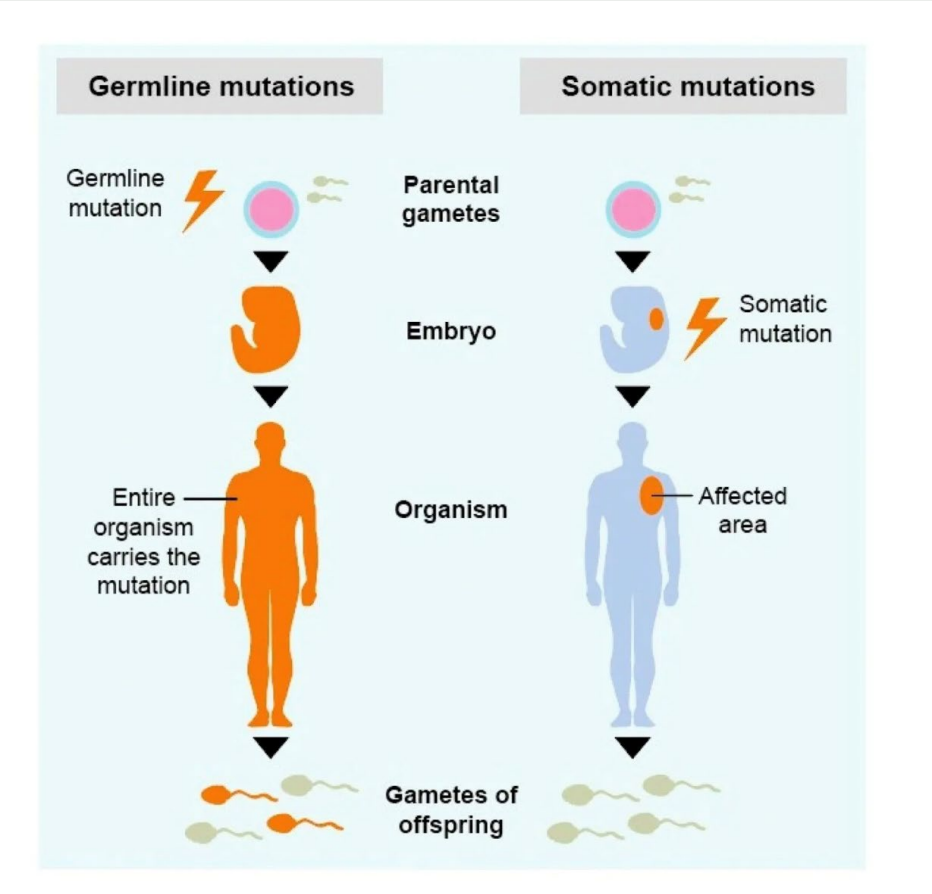
MLH1 1/1946

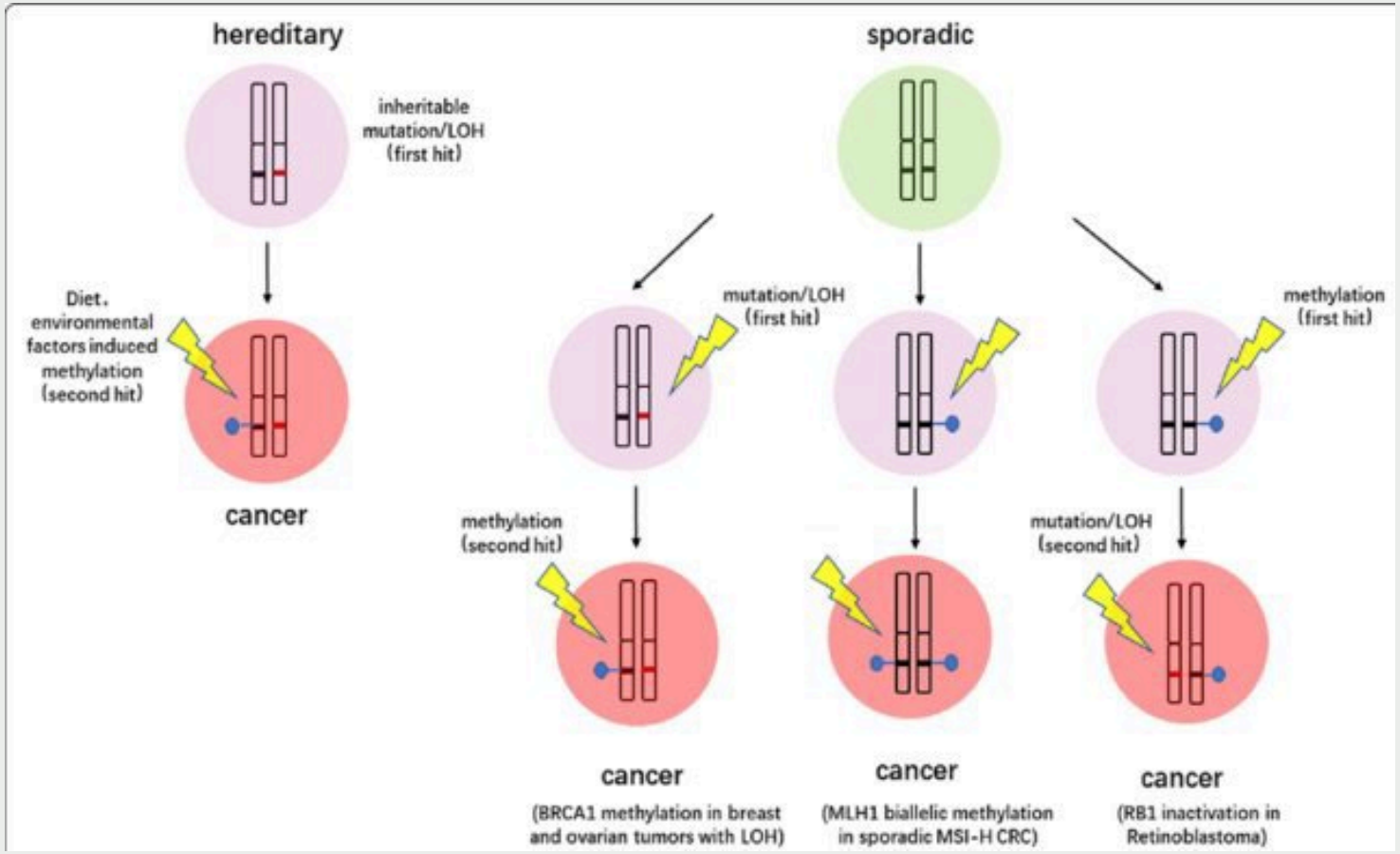
MSH2 1/2841

MSH6 1/758

PMS2 1/714

Rare EPM deletion


Germline mutations
Somatic mutations
Germline mutation
Parental gametes
Embryo
Somatic mutation
Entire organism carries the mutation
Organism
Affected area
Gametes of offspring


hereditary
inheritable mutation/LOH (first hit)
Diet, environmental factors induced methylation (second hit)
cancer
sporadic
mutation/LOH (first hit)
methylation (second hit)
cancer
(BRCA1 methylation in breast and ovarian tumors with LOH)
cancer
(MLH1 biallelic methylation in sporadic MSI-H CRC)
methylation (first hit)
mutation/LOH (second hit)
cancer
(RB1 inactivation in Retinoblastoma)

Hypertrophic Cardiomyopathy

Unexplained left ventricular wall thickness with maximal wall thickness > 15 mm in adult

If there is a positive family history of HCM or a pathogenic variant in the family is identified in one of the known Sarcomeric genes, the maximal wall thickness > 13 mm

Manifestation

Adolescence onset

Outflow obstruction

-1/3 no outflow obstruction

-1/3 outflow obstruction provoked by maneuver

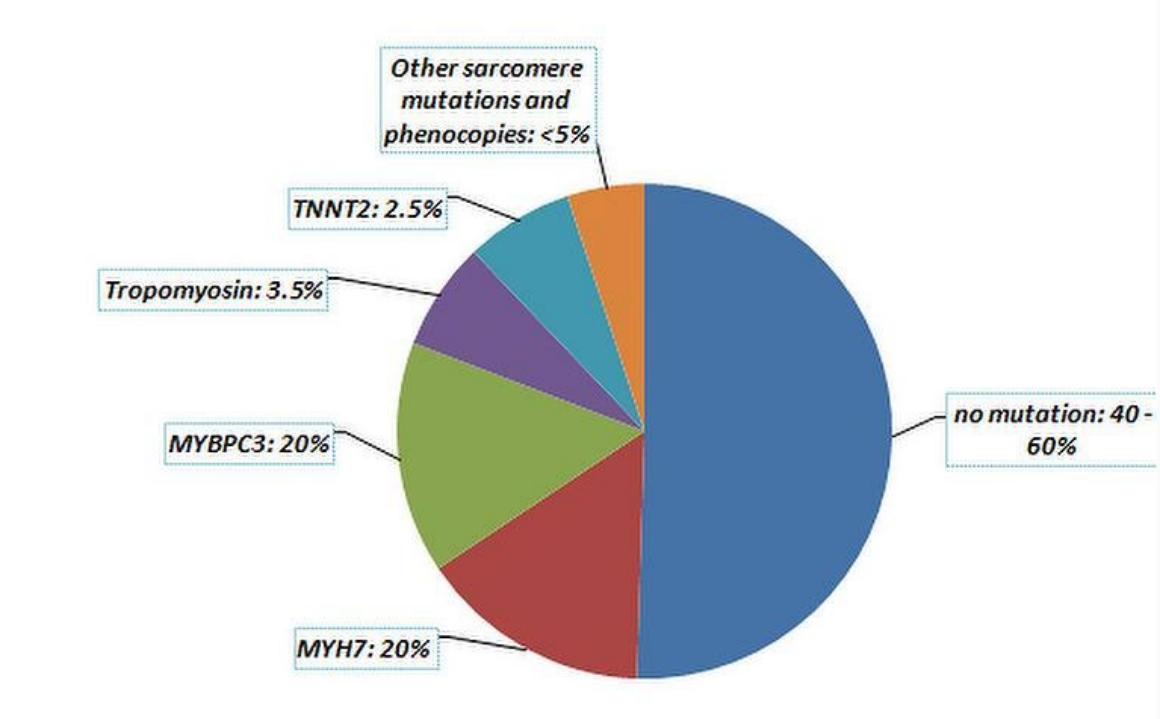
-1/3 outflow obstruction at rest

60% atrial fibrillation at 60 years old

5-10% progress to end stage heart failure

6 % in sudden cardiac death, cardiac arrest survivors

Genetic Testing



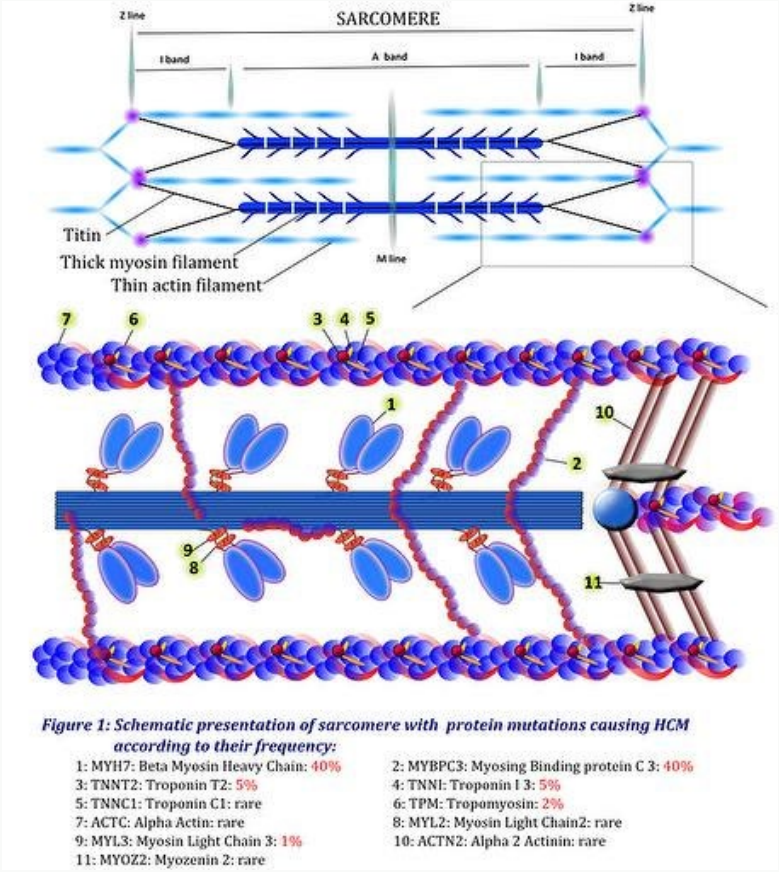
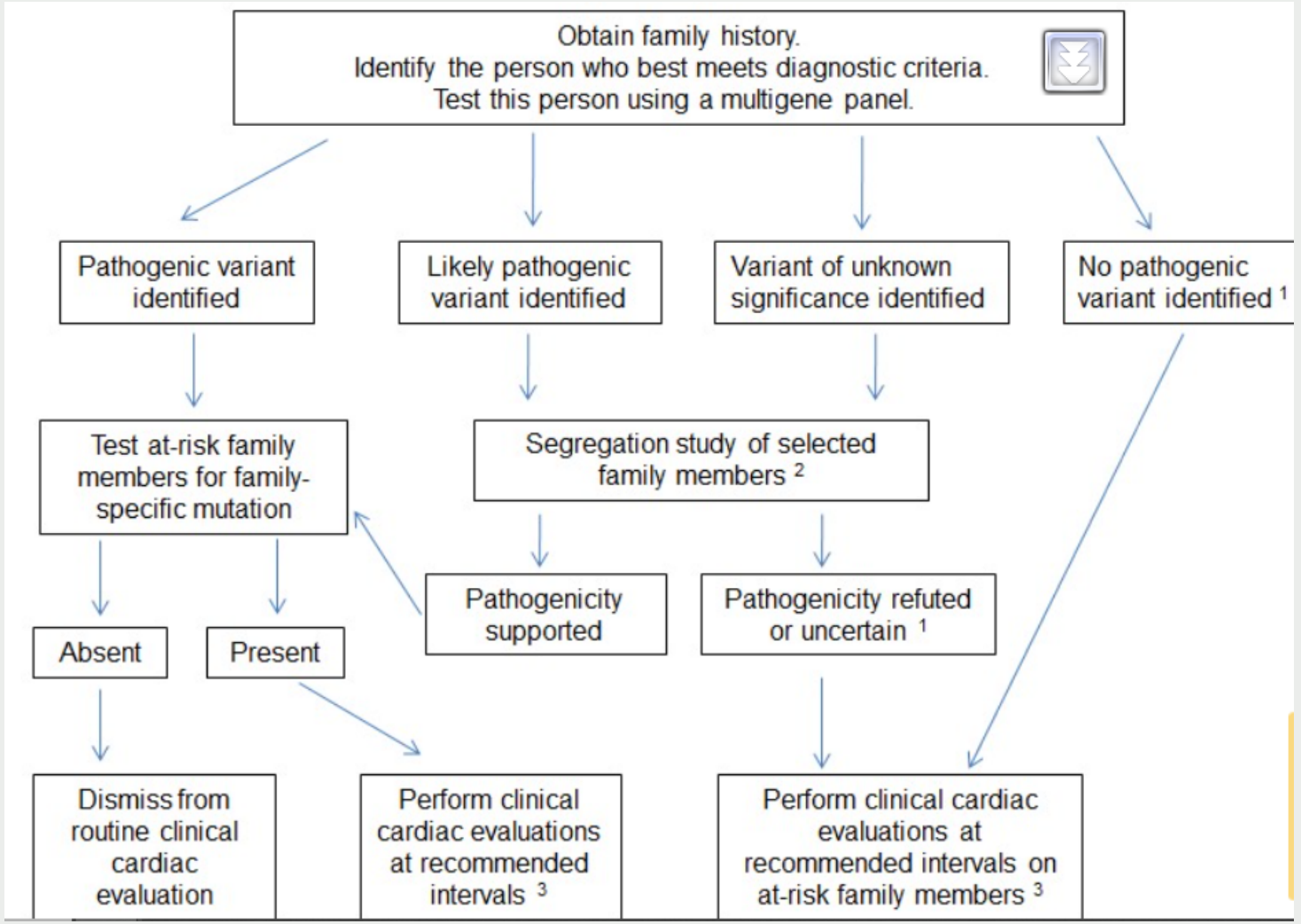


Figure 1: Schematic presentation of sarcomere with protein mutations causing HCM according to their frequency:

1: MYH7: Beta Myosin Heavy Chain: 40%
2: MYBPC3: Myosing Binding protein C 3: 40%
3: TNNT2: Troponin T2: 5%
4: TNNI: Troponin I 3: 5%
5: TNNC1: Troponin C1: rare
6: TPM: Tropomyosin: 2%
7: ACTC: Alpha Actin: rare
8: MYL2: Myosin Light Chain2: rare
9: MYL3: Myosin Light Chain 3: 1%
10: ACTN2: Alpha 2 Actinin: rare
11: MYOZ2: Myozenin 2: rare


Obtain family history.
Identify the person who best meets diagnostic criteria.
Test this person using a multigene panel.
Pathogenic variant identified
Likely pathogenic variant identified
Variant of unknown significance identified
No pathogenic variant identified 1
Test at-risk family members for family-specific mutation
Segregation study of selected family members 2
Pathogenicity supported
Pathogenicity refuted or uncertain 1
Absent
Present
Dismiss from routine clinical cardiac evaluation
Perform clinical cardiac evaluations at recommended intervals 3
Perform clinical cardiac evaluations at recommended intervals on at-risk family members 3

Benefit of Genetic Testing

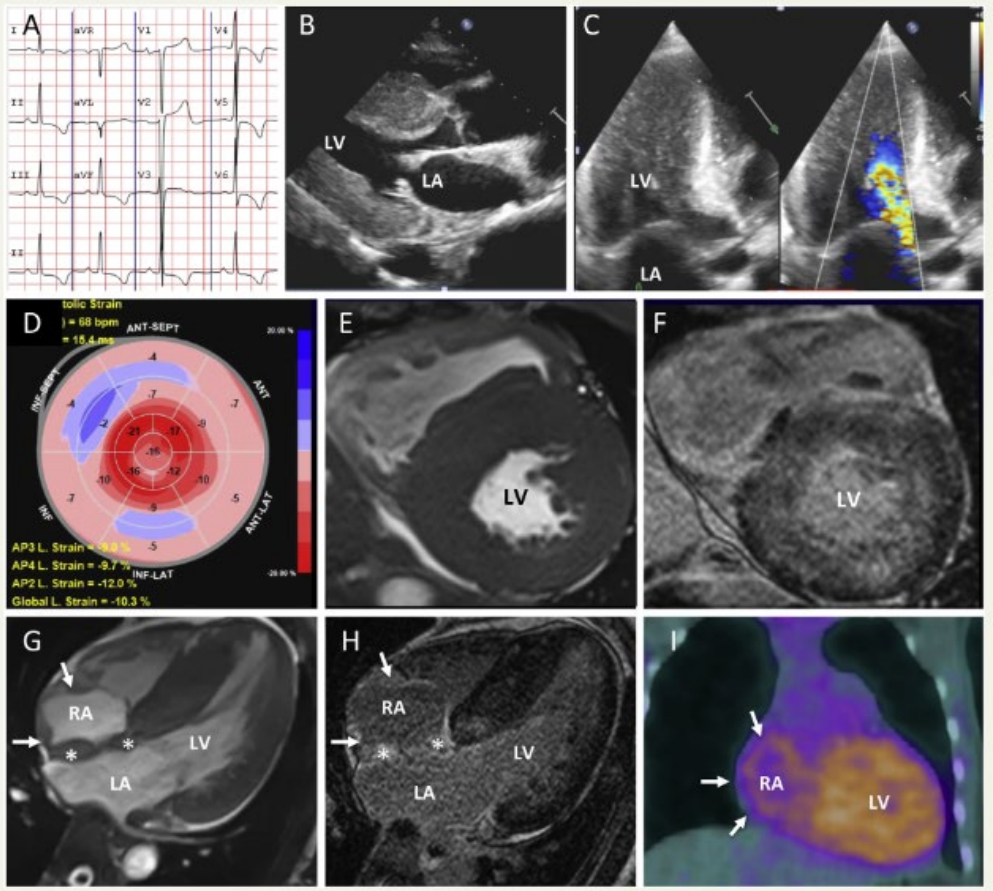
Benefits	Limitations
Confirm HCM even in ambiguous cases and before overt hypertrophy	Limited positive predictive value
Rule out non affected cases	In the absence of a known mutation, a negative test doesn't rule out HCM
Prenatal and preimplantation diagnosis	Limited clinical and prognostic contribution
	Test interpretation may be challenging

Genetic Status	Age of Asymptomatic Relative [1]	Risk for Developing HCM	When To Initiate Screening	Repeat EKG & 2D Echo [2]
Heterozygous for the familial HCM-related pathogenic variant	Children & adolescents	High [3]	At the time HCM is diagnosed in another family member	Every 1-2 yrs
	Adults			Every 3-5 yrs
Not heterozygous for the familial HCM-related pathogenic variant	Children & adolescents	Not at ↑ risk	May be discharged from cardiac surveillance	NA
	Adults			

Differential Diagnosis (Syndromic)

Internist should know

- Fabry Disease
- TTR Amyloidosis
- Noonan Syndrome and RASopathies spectrum disorder



Mavacamten: Mechanism of Action

Normal Sarcomere

Normal contractility
Effective relaxation

HCM Sarcomere

HCM Pathophysiology
Hypercontractility
Impaired relaxation
Altered myocardial energetics

HCM Sarcomere with Mavacamten

Attenuated hypercontractility
Improved compliance
Improved energetics

Mavacamten is a targeted inhibitor of cardiac myosin that reduces the number of myosin-actin cross-bridges and decreases contractility

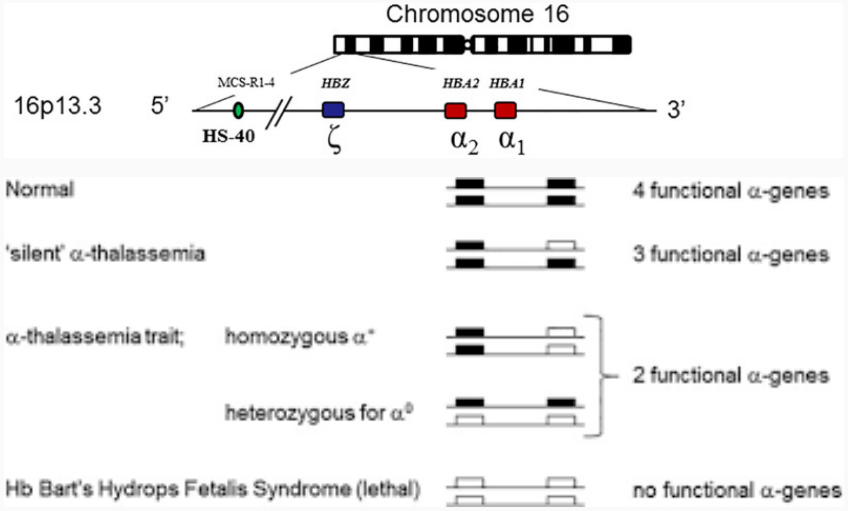
Game Changer? 89,500 USD annual cost

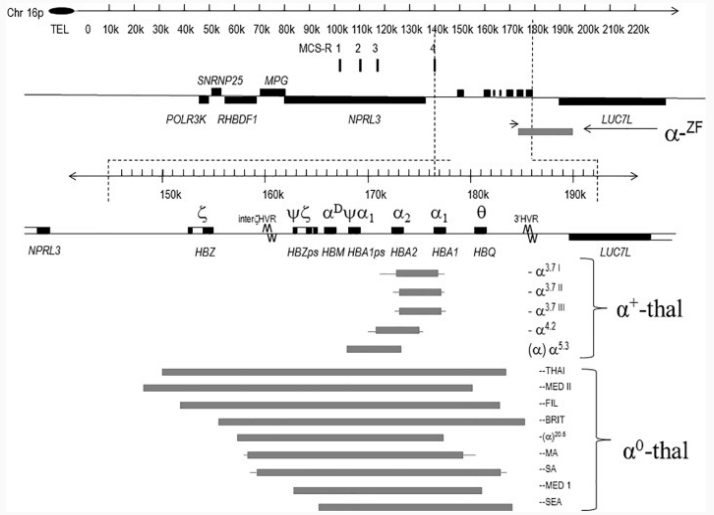
- Will remodeling be different in patients with sarcomeric variants versus those without?
- Will the extent of remodeling be related to the degree of LVOT obstruction?
- Will the favorable structural remodeling noted thus far result in improved outcomes in terms of development of atrial fibrillation and heart failure?
- Will the extent of remodeling be consistent in patients with recent-onset disease compared with patients with long-standing disease?
- Will patients with non-obstructive HCM derive a similar degree of favorable remodeling compared with those with oHCM?
- Will those with mid-cavitary obstruction and related apical aneurysms experience positive or negative cardiac remodeling?
- Could mavacamten, if introduced in children living with HCM, have similar favorable remolding and prevent disease progression and resultant high burden of adverse outcomes observed?[24]
- Could mavacamten be used as a preventative therapy in genotype-positive phenotype-negative patients

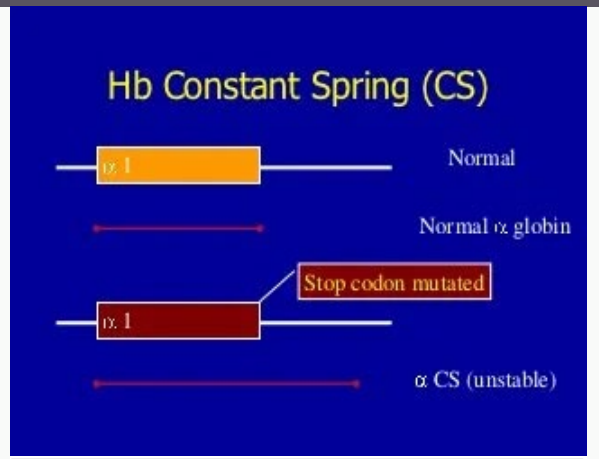
Prevalence

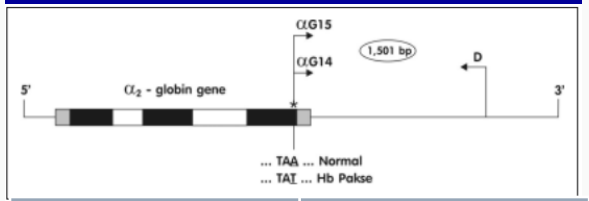
Echocardiographic Study	1/300
Genetic study (MYBPC3, MYH7, TNNT2)	nearly 1/100

Alpha-Thalassemia

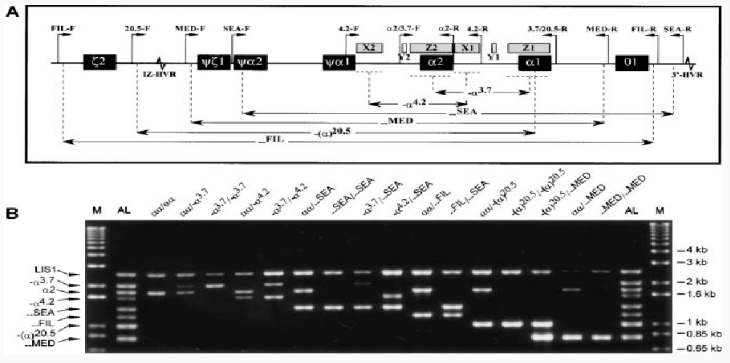






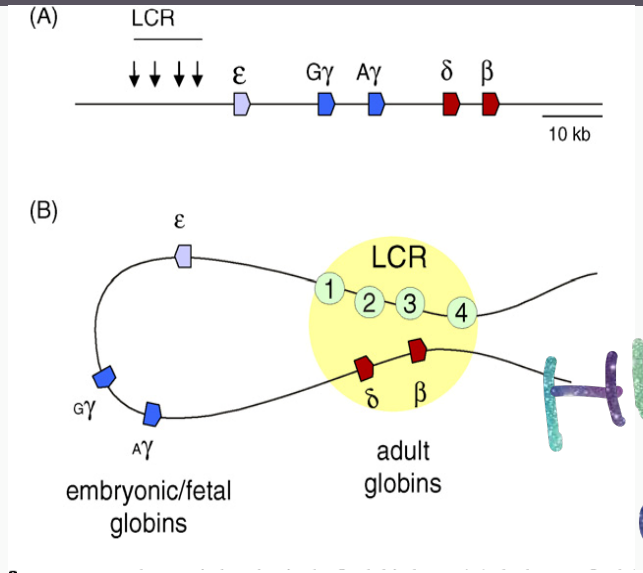


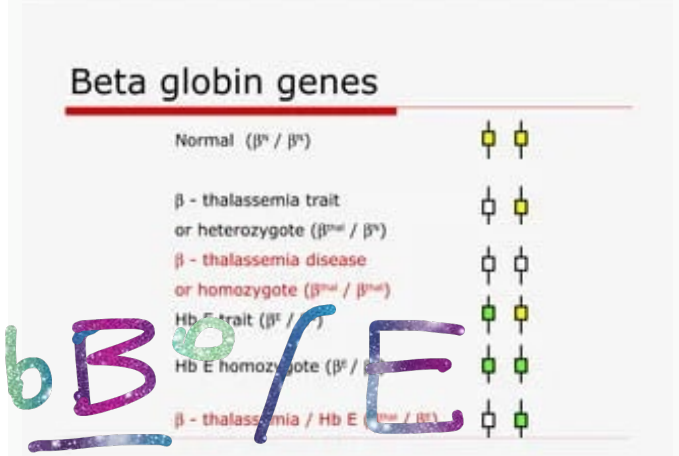
Hemoglobin Type [1]	Normal	Affected	
		Hb Bart syndrome [2]	HbH disease [3]
HbA	96%-98%	0	60%-90%
HbF	<1%	0	<1.0%
Hb Bart	0	85%-90%	2%-5%
HbH	0	0	0.8%-40%
HbA2	2%-3%	0	<2.0%
Hb Portland	0	10%-15%	0

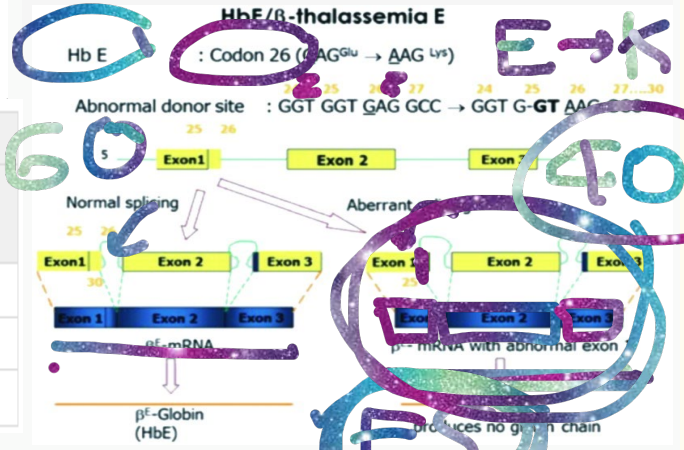


-SEA	3.3%
-3.7	2.1%
Hb_CS	5.7%
Hb_Pakse	0.5%

Beta-Thalassemia





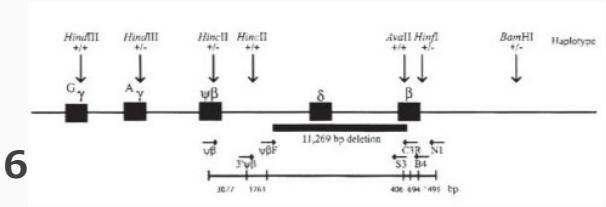


Hemoglobin Type	Normal [1]	Affected		Carrier
		β°-Thal Homozygotes [2]	β⁺-Thal Homozygotes or β⁺/β° Compound Heterozygotes [3]	β-Thal Minor
HbA	96%-98%	0	10%-30%	92%-95%
HbF	<1%	95%-98%	70%-90%	0.5%-4%
HbA_2	2%-3%	2%-5%	2%-5%	>3.5%

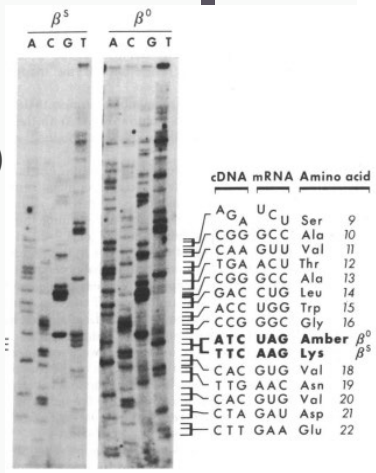
Hb E	α-Globin gene	Hb (g/dl)	MCV (fl)	Hb typing	Hb E (%)	HbBart's (%)	Hb F (%)	Clinical
Hb E heterozygote	αα/αα	12.8 ± 1.5	84 ± 5	EA	29 ± 2.3	-	0.9 ± 0.7	Normal
	−α/αα	13.1 ± 1.4	88 ± 4	EA	28 ± 1.5	-	0.7 ± 0.6	Normal
	−/αα	12.5 ± 1.4	77 ± 5	EA	21 ± 1.2	-	0.9 ± 0.4	Normal
	−/−α	9.1 ± 1.1	60 ± 3	EFA Bart's	13 ± 2.1	4.5 ± 1.9	2.2 ± 1.9	Thal intermedia (AEBart's disease)
Hb E homozygote	αα/αα	10.6 ± 1.2	65 ± 3	EF	88 ± 2.6	-	3.6 ± 1.6	Normal
	−α/αα	11.0 ± 1.6	65 ± 4	EF	87 ± 3.3	-	4.8 ± 3.7	Normal
	−/αα	10.5 ± 2.4	64 ± 7	EF	88 ± 5.7	-	3.8 ± 2.1	Normal
	−/−α	7.5 ± 0.8	60 ± 2	EF Bart's	81 ± 1.5	4.2 ± 1.1	6.4 ± 1.2	Thal intermedia (EFBart's disease)
Hb E β thalassemia	αα/αα	7.1 ± 1.4	59 ± 3	EF	58 ± 9.5	-	38 ± 11.7	Mild to severe disease
	−α/αα	8.5 ± 1.1	55 ± 3	EF	71 ± 7.5	-	24 ± 8.7	Mild disease
	−/αα	9.3 ± 0.5	52 ± 1	EF	84 ± 3.8	-	12 ± 2.5	Mild disease
	−/−α	7.6 ± 1.2	61 ± 2	EF Bart's	82 ± 2.5	1.5 ± 0.3	5.5 ± 0.7	Thal intermedia (EFBart's disease)

Beta globin gene variant

c.79 G>A (p. E27K) (HbE)		18% (291/1642)
c.52A>T (p.K18*)	(Beta0-17)	0.8% (13/1642)
c.126-129del (p.F42Lfs*19)	(FS41/42)	0.7% (11/1642)
c.92+1G>T	(IVS1+1)	0.2% (3/1642)
		ICS1 +5, FS 71/72



WGS (20%) -78 A-G, IVS2-6



β-Thalassemia Mutations in Thailand

Mutation	No. of Chromosomes (% frequency) β^{Th}/β^{Th}	β^{E}/β^{Th}	Total
Frameshift 41/42	11 (28.9)	48 (61.5)	59 (50.9)
−28 A-G	9 (23.7)	3 (3.9)	12 (10.3)
IVS-2 nt 654	6 (15.8)	7 (9.0)	13 (11.2)
β^0 17	3 (7.9)	9 (11.5)	12 (10.3)
IVS-1 nt 5	2 (5.3)	4 (5.1)	6 (5.2)
IVS-1 nt 1	0	2 (2.6)	2 (1.7)
Frameshift 71/72	0	1 (1.3)	1 (0.8)
Codon 35 TAC-TAA[a]	0	3 (3.9)	3 (2.6)
−86 C-G[a]	1 (2.6)	0	1 (0.8)
Codon 19 A-G[b]	2 (5.3)	0	2 (1.7)
Frameshift 14/15	0	1 (1.2)	1 (0.8)
Uncharacterized	4 (10.5)	0	4 (3.4)
Total	38	78	116

[a] Refers to previously described mutations.
[b] The A→G mutation in codon 19 was recently reported in the Malay population (Yang et al. 1989).

requencies of Different β-Thalassemia Mutations in Asians

Mutation	Frequency (%) Thais[a]	Chinese[b] (n = 93)	Indians[c] (n = 102)	Malaysians[d] (n = 41)
rameshift 41/42	50.9	48.3	11.8	12.2
-28 A-G	10.3	7.5	0	0
VS-2 nt 654	11.2	21.5	0	7.3
0 17	10.3	9.6	0	2.4
VS-1 nt 5	5.2	0	22.5	48.8
VS-1 nt 1	1.7	0	13.7	7.3
600-bp Deletion	0	0	20.5	0
Frameshift 8/9	0	0	19.6	0
β^0 15	0	0	4.9	0
Frameshift 71/72	.8	0	0	0
Codon 19 A-G	1.7	0	0	14.6
Codon 35 TAC-TAA	2.6	0	0	0
Frameshift 35	0	0	0	4.8
Frameshift 16	0	0	1.0	0
−88 C-T	0	0	2.0	0
−86 C-G	.8	0	0	0
CAP +1	0	0	2.0	0
Uncharacterized	3.4	12.9	2.0	2.4

https://globin.bx.psu.edu/globin/hbvar/

HbVar

A Database of Human Hemoglobin Variants and Thalassemia mutations

Information about hemoglobin variants (both pathological and nonpathological) and mutations that cause thalassemias

Search database

Other Resources

Summaries of mutation categories	Compound heterozygous phenotype	*NEW Most recent update	FAQ
FINDbase: for allele frequencies	BX Browser: UCSC Browser mirror with HbVar variants	LOVD: version of HbVar plus other related genes	dbSNP entries associated with HbVar
SNP coordinate converter	Difference in mass chart	NCBI Reference sequences: NG_000007.3, NG_000006.1	User counts

About HbVar

Contact us: <hbvar-curators@bio.cse.psu.edu>

Curators

Citing this resource

Giardine B, Borg J, Viennas E, Pavlidis C, Moradkhani K, Joly P, Bartsakoulia M, Riemer C, Miller W, Tzimas G, Wajcman H, Hardison RC, Patrinos GP. Updates of the HbVar database of human hemoglobin variants and thalassemia mutations. Nucleic Acids Res. 2014 Jan;42 (Database issue):D1063-9.

Familial Hypercholesterolemia

Clinical Criteria Study: 1/250

Genetic Study: *LDLR* c.1056C>A (p.Cys352*) 10/1559,

All PV/LPV 15/1559 -> 1%

Clinical Diagnostic Criteria for FH

F+H=FH

Possible FH by Simon Broome

SIMON BROOME CRITERIA

T-C > 290 mg/dl or LDL-C > 190 mg/dl in adults OR

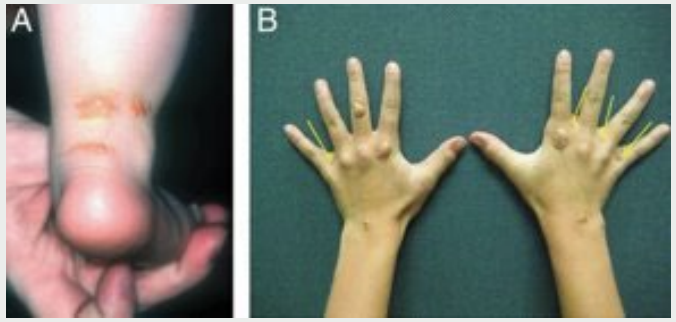
T-C > 260 mg/dl or LDL-C >155 mg/dl in pediatrics

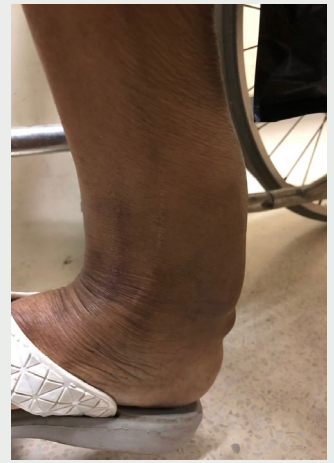
With

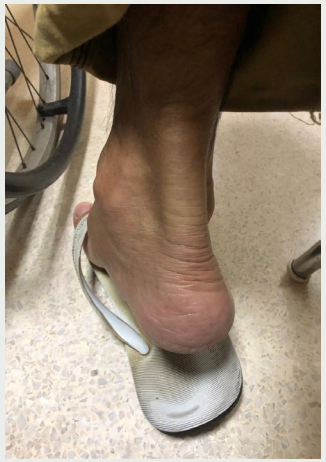
Tendon Xanthomas in the patient or in a FDR or SDR

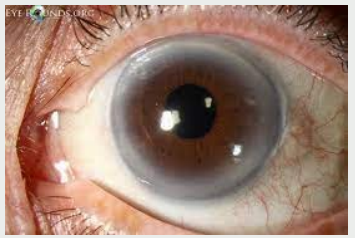
Or

DNA-based of LDLR mutation (LOF), APOB (LOF), or PCSK9(GOF)



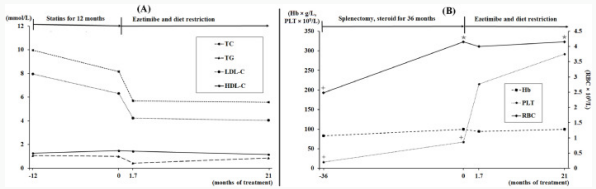


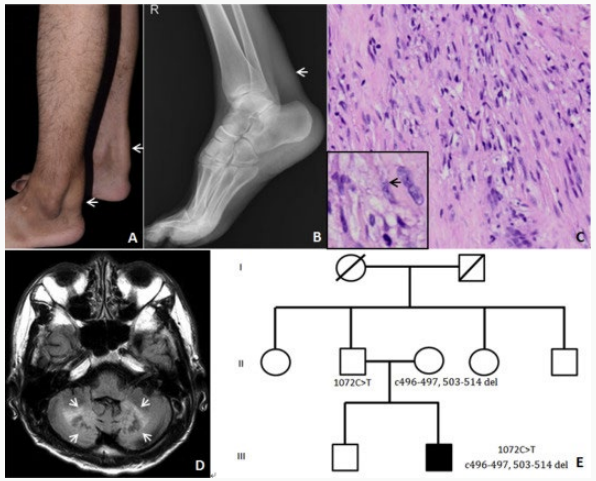


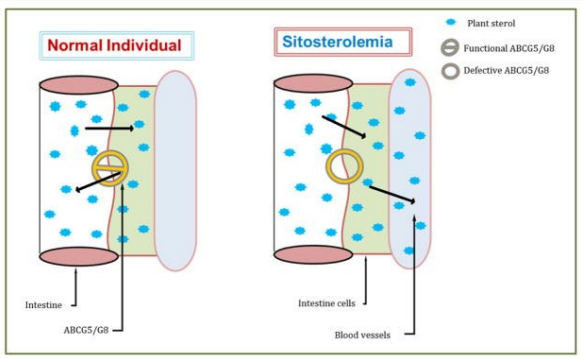


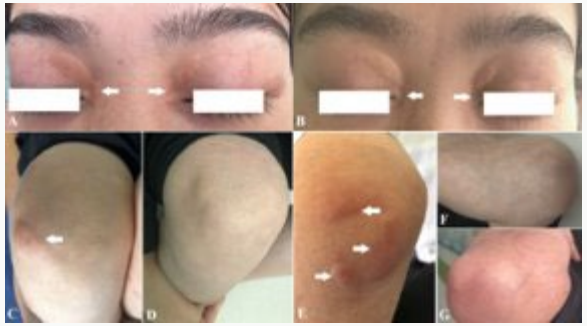
Differential Diagnosis

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Similar to FH	Distinguishing from FH
ABCG5 ABCG8	Sitosterolemia	AR	Xanthomas; susceptibility to early-onset CAD. Some persons may present w/↑ plasma cholesterol/LDL-C (often presents in childhood).	Hematologic abnormalities (hemolytic anemia, thrombocytopenia, stomatocytes); xanthomas in childhood (particularly in absence of hyperlipidemia in parents); poor response to statins
APOE	p.Leu167del-related AD hypercholesterolemia [1]	AD	Persons may present w/↑ LDL & ↑ risk of CAD.	Splenomegaly, sea-blue histiocytosis, thrombocytopenia, & ↑ triglycerides reported in some p.Leu167del heterozygotes
	Hyperlipoproteinemia type III (familial dysbetalipoproteinemia [FD]) (OMIM 617347)	AR AD [2]	Persons w/predisposing *APOE* variants are at risk of developing xanthomas (more commonly cutaneous & tuberous) & premature CAD. Most common *APOE* genotype assoc w/FD: homozygosity for E2 allele (p.Arg176Cys); however, >30 *APOE* variants have been assoc w/FD. [2]	Persons w/FD are at risk of developing ↑ triglycerides.
CYP27A1	Cerebrotendinous xanthomatosis (CTX)	AR	Xanthomas	Dementia, ataxia, & cataracts; normal LDL-C
LIPA	Lysosomal acid lipase deficiency	AR	↑ LDL-C; risk of CAD	• In infantile onset (Wolman disease): ↑ triglycerides, malnutrition, hepatosplenomegaly, liver disease, adrenal cortical insufficiency • In adult onset (cholesterol-ester storage disease): hepatosplenomegaly &/or ↑ liver enzymes, ↑ triglycerides









Dutch Lipid Clinic (>8)

FH-FDR with tx, or ac (2), FDF with known premature CAD, CVD, PVD (1)

CH- premature CAD (2), premature CVD or PVD (1)

PE – tendinous xanthoma (6), arcus cornealis < 45 years (4)

CL – LDL-C > 330 (8), > 250 (5), > 190 (3), >155 (1)

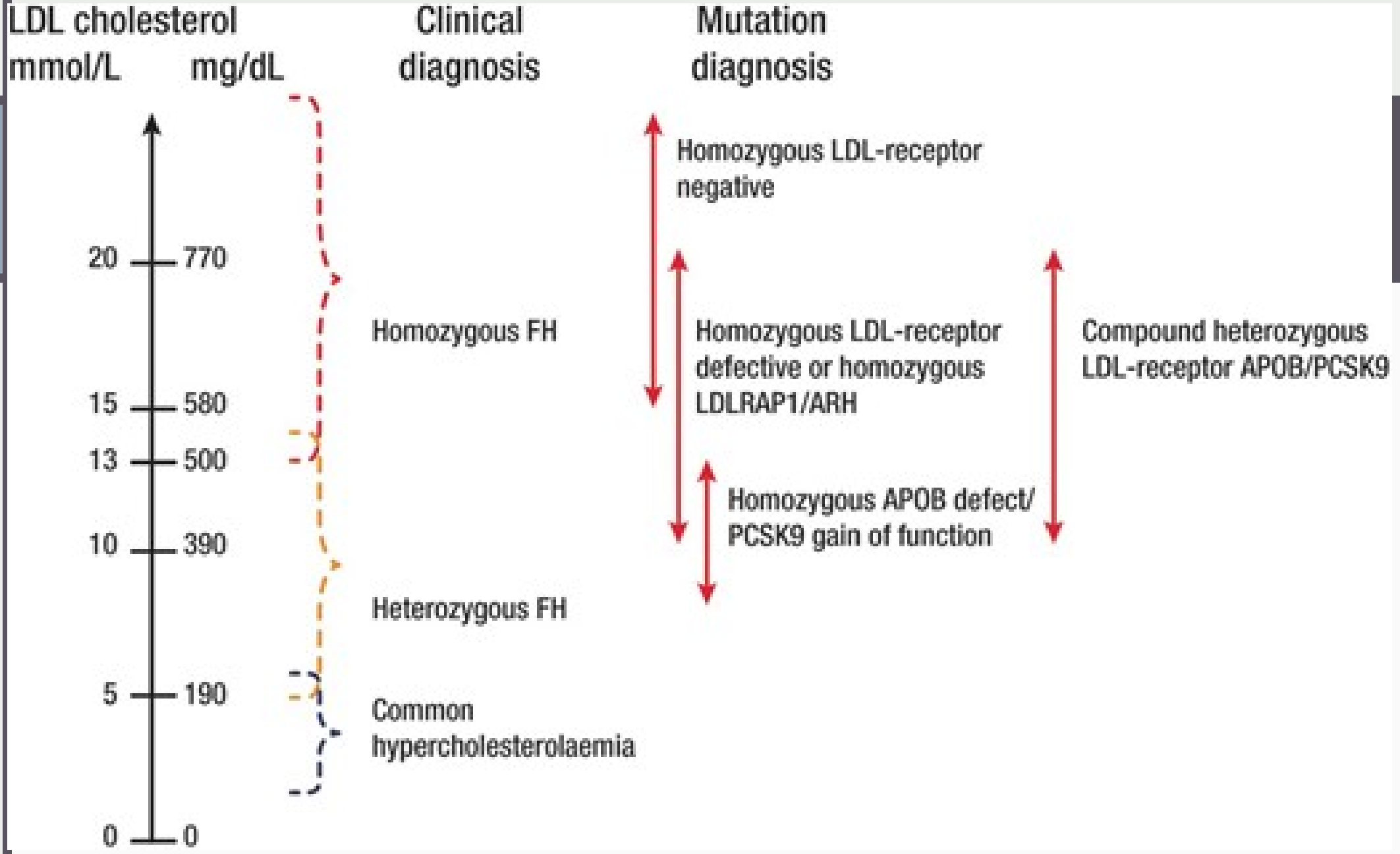
DNA – LDLR, apoB, PCSK9

MEDPED

Age	Total Cholesterol (LDL-C) concentrations, mg/dL			
	First-degree relative	Second-degree relative	Third-degree relative	General population
<18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
40 +	290 (205)	300 (215)	310 (225)	360 (260)

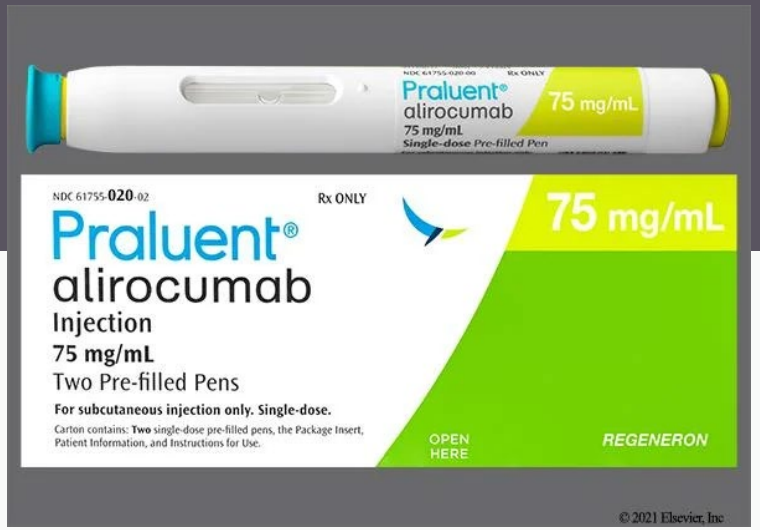
Homozygous Familial Hypercholesterolemia

Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus
OR
An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
○ Cutaneous or tendon xanthoma before age 10 years
or
○ Untreated elevated LDL-C levels consistent with heterozygous FH in both parents
* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

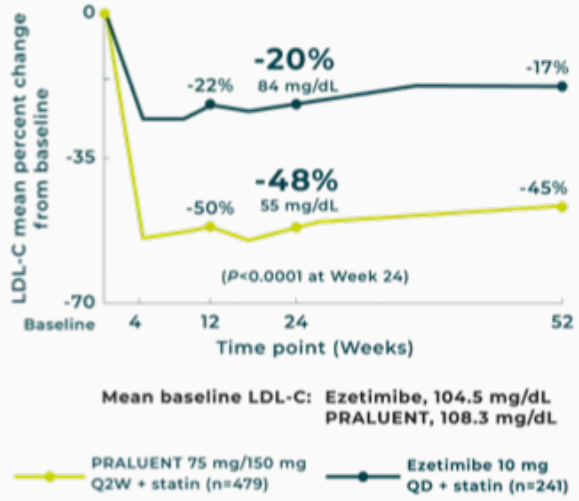

LDL cholesterol
mmol/L
mg/dL
Clinical diagnosis
Mutation diagnosis
20
770
15
580
13
500
10
390
5
190
0
0
Homozygous FH
Heterozygous FH
Common hypercholesterolaemia
Homozygous LDL-receptor negative
Homozygous LDL-receptor defective or homozygous LDLRAP1/ARH
Homozygous APOB defect/ PCSK9 gain of function
Compound heterozygous LDL-receptor APOB/PCSK9

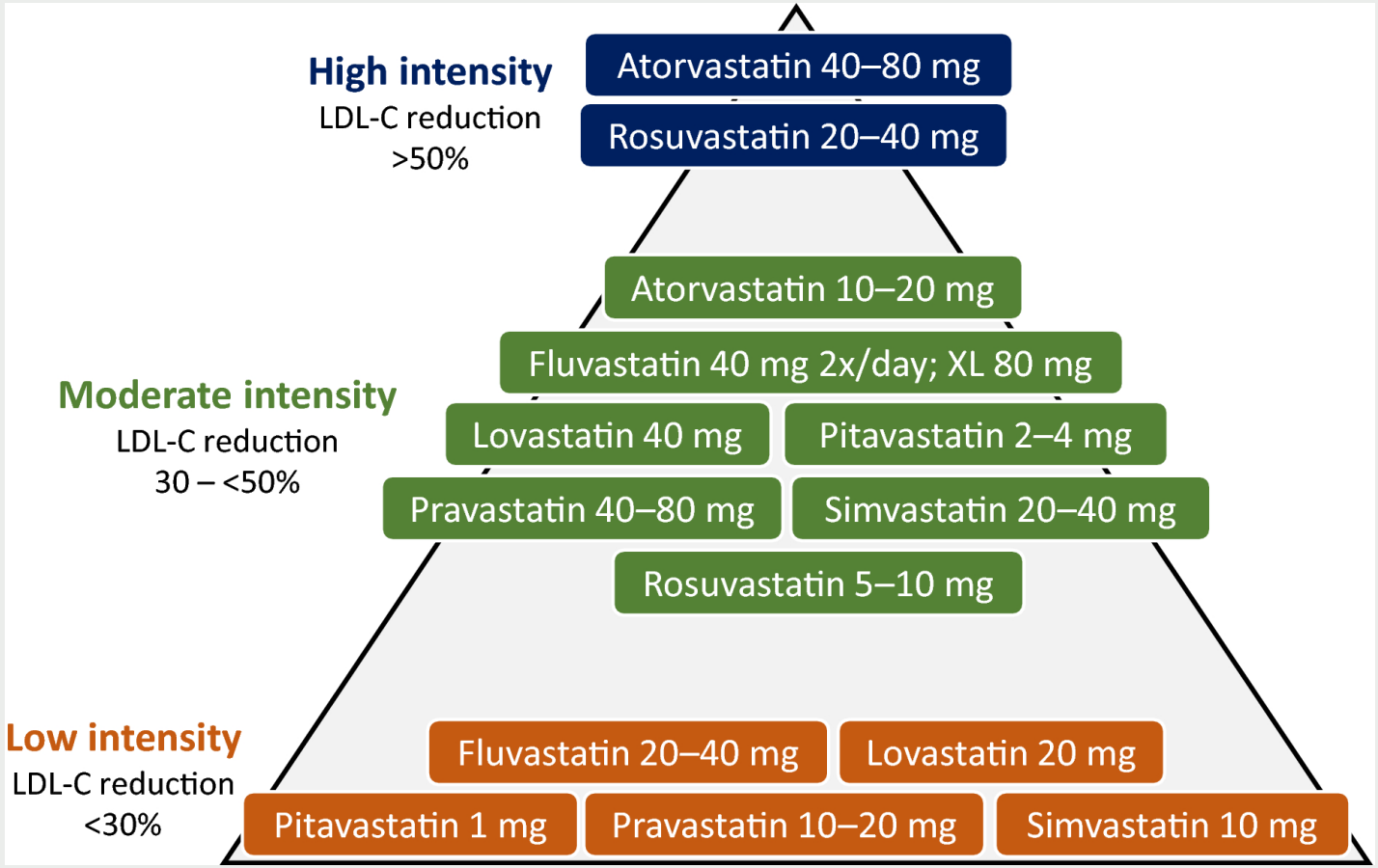
Medication Treatments

Class	Primary (1^O) and Secondary (2^O) Mechanism of Action	LDL-Lowering Response
Statins	↑ LDLR activity (1^O) Inhibition of cholesterol biosynthesis through HMG-CoA reductase	50% [1, 2]
Cholesterol absorption inhibitors (ezetimibe)	↓ cholesterol absorption (1^O) ↑ LDLR activity (2^O)	15% [1, 3]
MTP inhibitor (lomitapide) [4]	↓ microsomal triglyceride transfer protein activity (1^O) Inhibition of LDL production (2^O)	50% [5]
PCSK9 inhibitors (alirocumab, evolocumab, inclisiran)	↓ LDLR degradation	50% [6]
Bile acid sequestrants (cholestyramine, colesevelam)	↓ bile acid reabsorption (1^O) ↑ LDLR activity (2^O)	15% [1, 3]
Stanol esters	↓ cholesterol absorption (1^O) ↑ LDLR activity (2^O)	10% [1, 3]
Bempedoic acid	↑ LDLR activity (1^O) Inhibition of cholesterol biosynthesis by inhibiting ATP-citrate lyase	15%
Evinacumab [4]	Inhibition of ANGPTL3, which results in ↑ lipoprotein lipase activity ↓ VLDL	50%



75mg SC q 2 weeks
8000 THB/dose
192,000 THB/year




High intensity
LDL-C reduction
>50%
Atorvastatin 40–80 mg
Rosuvastatin 20–40 mg
Moderate intensity
LDL-C reduction
30 – <50%
Atorvastatin 10–20 mg
Fluvastatin 40 mg 2x/day; XL 80 mg
Lovastatin 40 mg
Pitavastatin 2–4 mg
Pravastatin 40–80 mg
Simvastatin 20–40 mg
Rosuvastatin 5–10 mg
Low intensity
LDL-C reduction
<30%
Fluvastatin 20–40 mg
Lovastatin 20 mg
Pitavastatin 1 mg
Pravastatin 10–20 mg
Simvastatin 10 mg

>90% of FH remain undiagnosed


TOP
HITS

Glucose 6 Phosphate Dehydrogenase Deficiency

From genetic study:

-10% of Thai men has G6PD deficiency or about 3 million men

- 20% of Thai women are the carrier (that can be symptomatic) of pathogenic variant in G6PD or about 1.5 million women

- 127/1642 in total

-> 10,000 boy born with G6PD deficiency each year

-> 20% develop neonatal jaundice required phototherapy (3xrisk, F 2X risk)

-> > 2,000 boy required phototherapy as a result of G6PD deficiency

G6PD deficiency vs P. vivax

Prevalence of G6PD deficiency

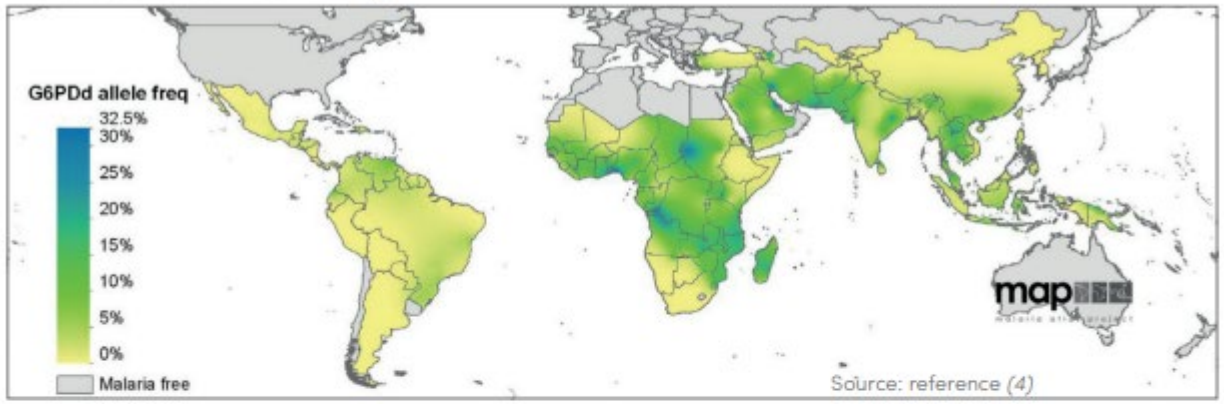
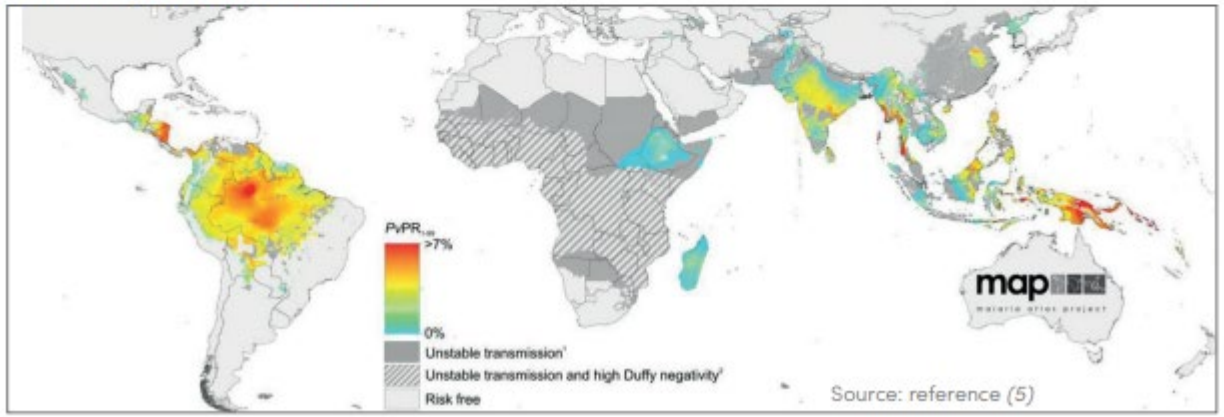


FIGURE 2
Endemicity of *P. vivax* in 2010



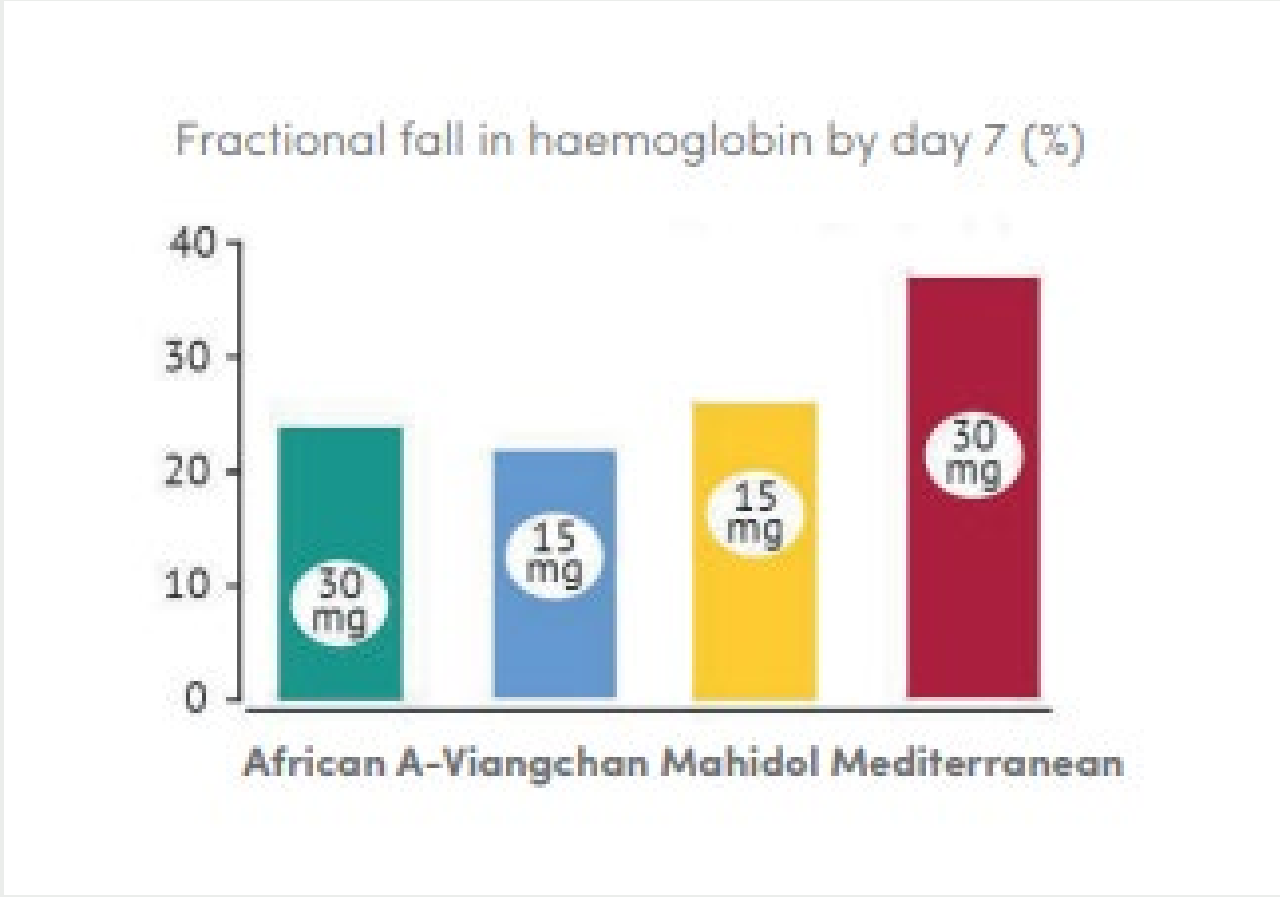
Drug induced hemolytic anemia

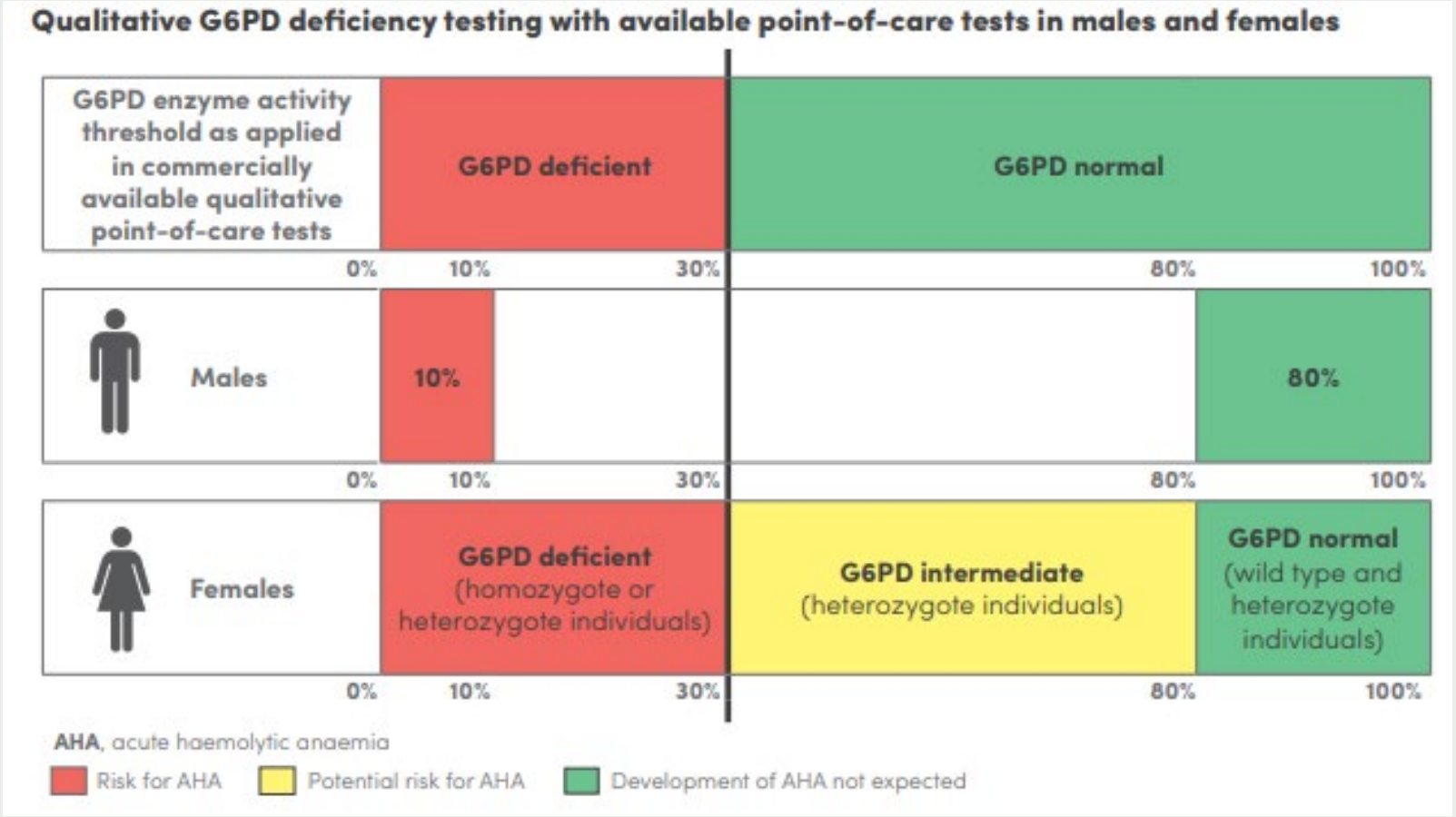
Acute hemolysis can occur in a G6PD deficient person who is exposed to antimalarials from the 8-aminoquinoline family.

Primaquine remains the only medicine available against chronic infection and relapsed caused by P. vivax and P. ovale and the tranmission of P. falciparum

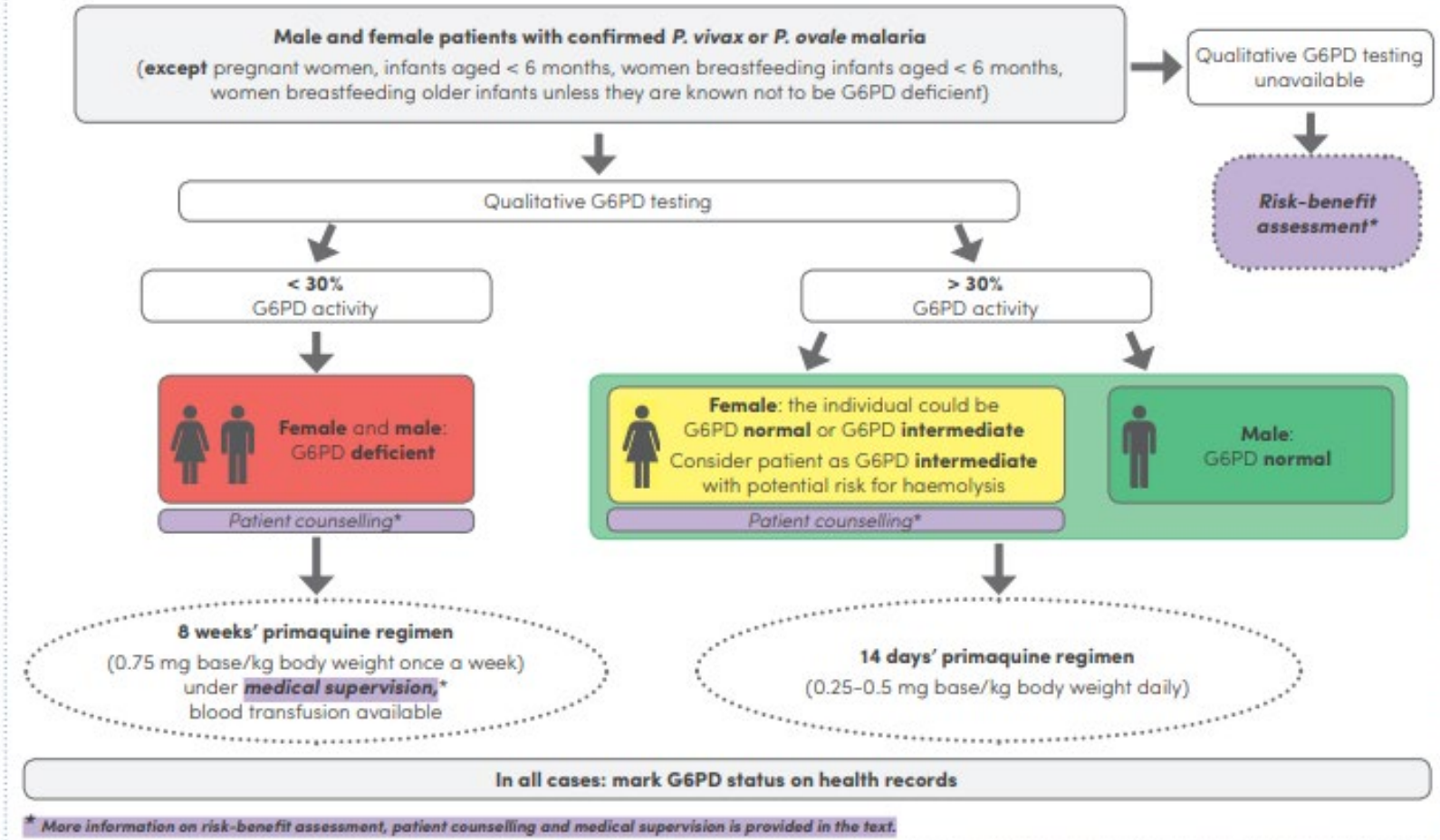
10,000 Cases of malaria infection annually in Thailand, 8000 of these are P vivax cases of these > 500 cases can develop severe hemolysis required blood transfusion

This is in line with the policy adopted by the government of Lao PDR to prescribe primaquine only after the G6PD status of the patient is identified <- WHO Recommendation 2014


Fractional fall in haemoglobin by day 7 (%)
40
30
20
10
0
30 mg
15 mg
15 mg
30 mg
African A-Viangchan Mahidol Mediterranean


Qualitative G6PD deficiency testing with available point-of-care tests in males and females
G6PD enzyme activity threshold as applied in commercially available qualitative point-of-care tests
G6PD deficient
G6PD normal
0%
10%
30%
80%
100%
Males
10%
80%
Females
G6PD deficient (homozygote or heterozygote individuals)
G6PD intermediate (heterozygote individuals)
G6PD normal (wild type and heterozygote individuals)
AHA, acute haemolytic anaemia
Risk for AHA
Potential risk for AHA
Development of AHA not expected

Algorithm for qualitative point-of-care testing and safe administration of primaquine to prevent relapse of *P. vivax* or *P. ovale* malaria in male and female patients



Other drug with definite association

Primaquine

Sulfonamides

Dapsone

Co-trimoxazole

Napthalene

Drugs with possible association

Chloroquine

Glibenclamide

Aspirin

Ciprofloxacin

Vitamin K and Vitamin C

Infection-induced hemolytic anemia

Hepatitis A

Hepatitis B

Cytomegalovirus

Dengue virus

Typhoid fever

Pneumonia

Favism

Raw > Dried or Frozen

Maternal consumption -> breast feeding

24 hours after eat

Hemoglobinuria severe > drug or infection induced

Chronic non spherocytic hemolytic anemia (CNSHA)

G6PD Bangkok (825G>C)

G6PD Bangkok Noi (1502T>G)

Can be co-incidence with other common red cell disorders: Thalassemia, Hereditary Spherocytosis

INDICATION

Acute hemolysis after drugs, infections or fava bean ingestion

Family history of neonatal jaundice, splenomegaly or gall stone

Personal history of severe neonatal hyperbilirubinemia

Malaria endemic area before administer antimalarial drug - primaquine

When to test

Carrier screening

Newborn screening *********

At risk family screening

Symptomatic screening

G6PD Variants

Vientiane c.961 G> A (p.Val321Met)	55/1642
Mahidol c.577G>A (p. Gly193 Ser)	33/1642
All	127/1642

Top Five Genetic Diseases

1. G6PD deficiency
2. Familial Hypercholesterolemia
3. Thalassemia
4. Hypertrophic Cardiomyopathy
5. Hereditary Breast-Ovarian Cancer Syndrome and Lynch syndrome

Case 1

Proband – Asymptomatic female 38 yo – no children

Family history of Cancer

Mom: 58 yo – endometrium carcinoma

Younger brother 35 yo – dx stomach carcinoma 30 yo

Second opinion, self-referral: BRCA test was recommended, Prophylactic mastectomy

?

Case 2

Proband: male 36 yo – asymptomatic, son 7 yo, daughter 4 yo

Family history – father died 48 yo from CA stomach, younger sister died 28 yo from CA ovary

Self referral- Direct to consumer genetic testing (Lazada - ****) – BRCA1 positive – application,**

Wellness result ****

?

Case 3

Oncologist consult a case with advanced breast cancer with Family history of breast cancer (young onset, bilateral – older sister)

Genetic testing (previous): VUS BRCA1

Q: any further genetic test, or interpretation of previous result

- **Patient eligible for PARP inhibitor?**
- **……**
- **BRCA1 variant is reclassified to likely pathogenic -> she is eligible for PARPi**
- **Older sister -> recalled for genetic testing -> daughter 35 yo -> single**
- **Multiple gene panel testing is chosen**
- **Pathogenic BRCA1 variant – different one**