The Amish - Culture, Medical Care, & Genetic Disorders

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So much care, so close.

Amish

Photo Janet Kruk

Descended from several hundred families who came to US in 1700s

- Closed community
  (few marry into community)
- Large families – average seven children
- Population doubles every 20 years

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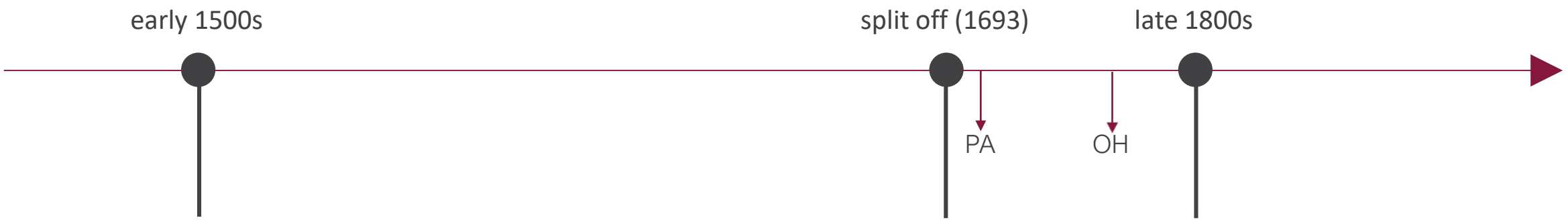
Amish

State	2019 Population	% of the total US Amish population, 2019
Pennsylvania	79,200	23.5%
Ohio	**76,195**	**22.6%**
Indiana	**57,430**	**17.1%**
Wisconsin	**22,020**	**6.5%**
New York	20,595	6.1%
Michigan	**16,410**	**4.9%**
Missouri	13,990	4.2%
Kentucky	**13,345**	**4.0%**
Iowa	9,980	3.0%
Illinois	**7,730**	**2.3%**
Minnesota	**4,680**	**1.4%**
Total (all States)	336,235	

States with >1%: TN, KS, DE, MD, VA, ME, MT, OK, CO, NE, WV, MS, NC, AK, WY, FL, SD, TX, VT, ID and Canada

"Amish Population Profile, 2019". Elizabethtown College, the Young Center for Anabaptist and Pietist Studies. Retrieved August 7, 2019.

Differentiation



Anabaptists

Mennonite (1525)

German & Dutch speaking Europe

No early baptism

Persecution

Amish

shunning

more conservative

Hutterite

Dakotas
central
Canada

Amish came to North America in two waves—in the mid-1700s and again in the first half of the 1800s. Their first settlements were in southeastern Pennsylvania. Eventually they followed the frontier to other counties in Pennsylvania, then to Ohio, Indiana, and to other Midwestern states. The first Amish people in Ohio arrived in the early 1800s.

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Early philosophical beliefs

- Separation of church and state
- Resistance to public education
- Nonviolence
  (alternative military service)
- Opposition to slavery

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Amish culture today

- Church at individual family homes (every other Sunday)
- “No Sunday sales”
- Marriage at or after age 21
- Divorce prohibited
- School through 8th grade

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Amish culture today

- Settlements centered around “church districts”
- Each has its own rules and dress
- “Plain” in dress; communal life
- Pridefulness, individuality discouraged
- Variability in communities is the rule*

Amish culture today

- Language – “Pennsylvania Dutch” (English second language)
- Transportation* – horse & buggy locally; hired drivers ($1 per mile) (travel for weddings, funerals common)
- No electricity* – challenges with medical equipment
- No telephones or computers* (prolific letter writers)

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Taxes

- Pay all state and local taxes
- Do not pay Social Security tax
- Sign “form 4029” at age 18
- Are not eligible for Medicare, Social Security, Medicaid

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Insurance

- Do not purchase insurance (homeowners, life, disability)
- No private health insurance
- No Medical assistance (form 4029)

Health care financing

- Pay cash, which limits health care
- Shop around
- Medical tourism common
- Ask discerning medical questions
  - "What do you anticipate finding with an echo; how will it affect my care?"

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Medical practices

Preference is for natural healing & trusted remedies

- Immune boosters, liver flushes, tinctures, herbs, homeopathics
- Chiropractic heavily used (Ortman Clinic)
- Chelation, magnetic therapy, cranial treatments, alternative therapies

Western medicine often used late in an illness

- Our views of superiority viewed with some skepticism

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So what is a (Western) doctor to do?

- Focus on service, not conversion to "our faith" (Western medicine)
- Be practical & conservative with testing
- Good *clinical* medicine – understand probability assessment in differential diagnosis
- Educate and give recommendation, but offer alternatives…
- Accept choices which would not be your first choice (have I been clear in my communication?)

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Pregnancy and Childbirth in the Amish

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Pregnancy in Amish

- Family and church are center of Amish life
- Birth control is almost never used
- Family size large
  (average of seven children)

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Location of deliveries

- Generally home births
- Birthing center, when available
- Hospital births are almost never electively chosen

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Attendants at birth

Attendant	Likelihood of Newborn Screen
Amish midwife	Variable
Licensed midwife	High
Grandmothers	Low
Husband	Low

History of the Birthing Center

- Recognition of birthing complications
- Proposal for hospital-based birthing center
- Birth in clinic “by accident” 1993
- Addition of ultrasound
- Cost
  - $650 in 1993
  - $1350 in 2018
    (includes all prenatal care; US; labs; delivery;
    PP home visit at 24-48 hours for Newborn
    Screen, congenital heart screen; hearing screen)

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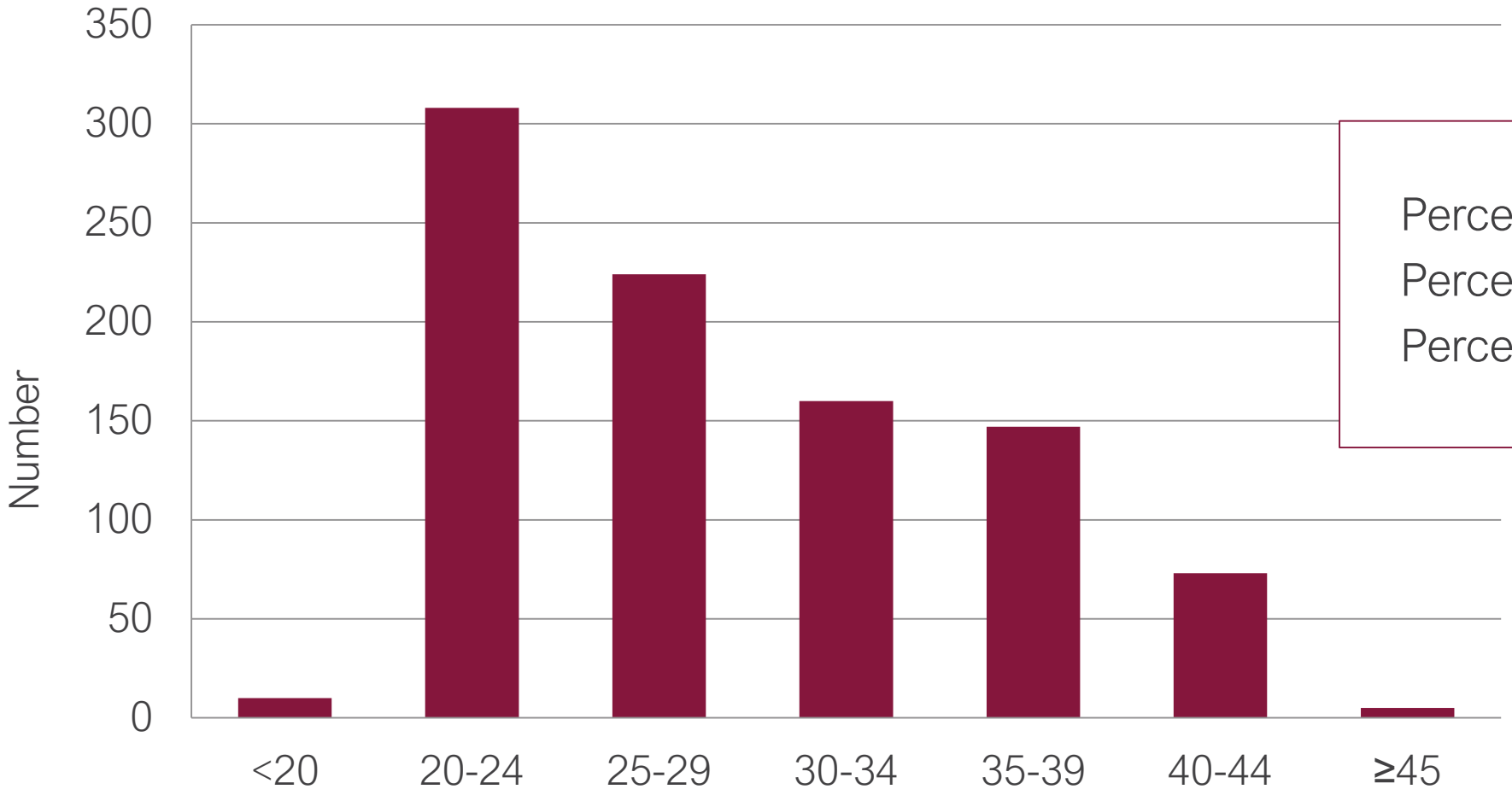
Maternal age



Percent under 21	3.3%
Percent 35 and older	24%
Percent 40 and older	8.4%

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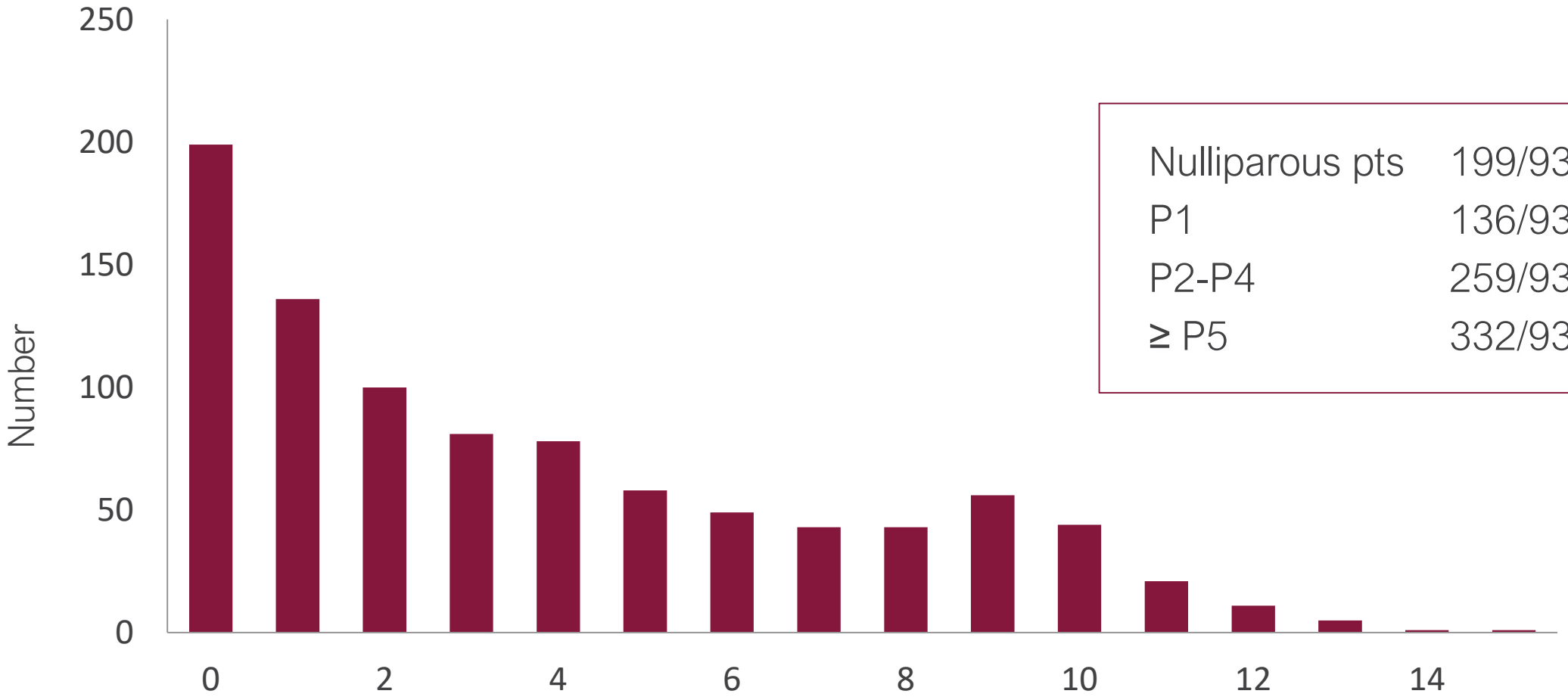
Maternal parity



Nulliparous pts	199/936	21.0%
P1	136/936	14.5%
P2-P4	259/936	27.5%
≥ P5	332/936	35.5%

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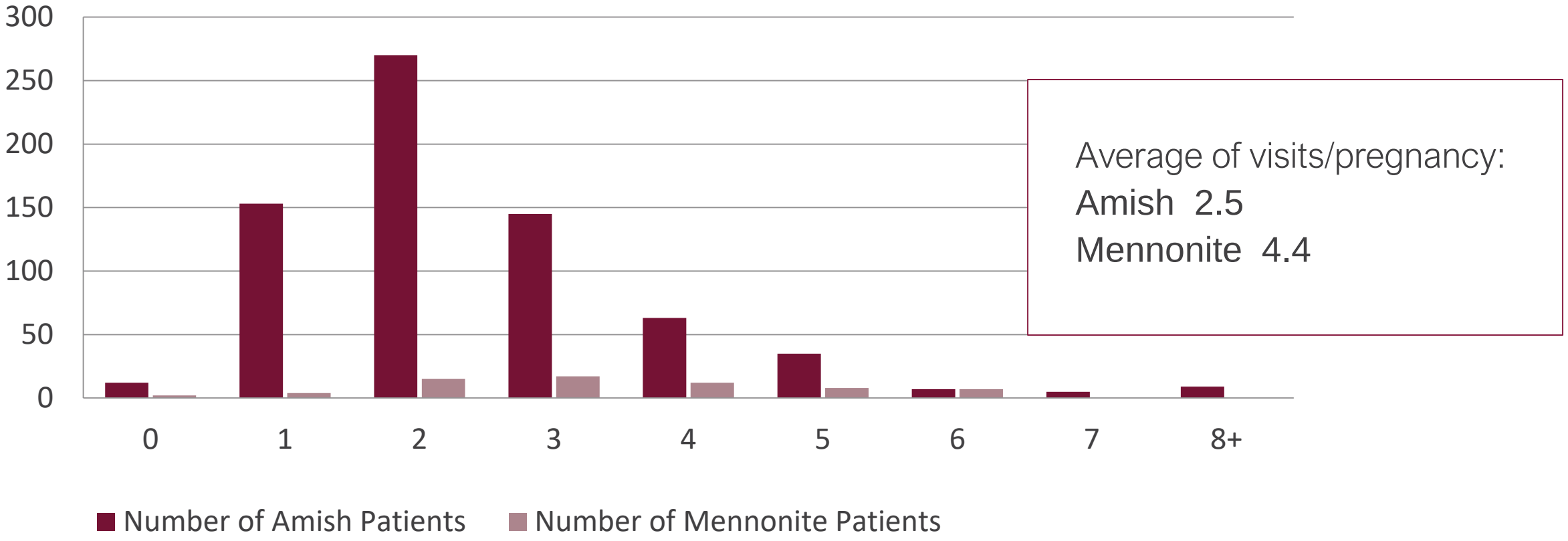
Prenatal visits



Average of visits/pregnancy:
Amish 2.5
Mennonite 4.4

C-sections

	Cases	Rate of C-section
Planned clinic births	28 of 839	3.4%
High risk “transfer in” patients	7 of 88	8.0%
Overall C-section rate	35 of 927	3.8%

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Vaginal Birth After C-section (VBAC)

	Success Rate	Total
Primary	25/28	89%
Subsequent	64/65	98%
Total	**89/93**	**95%**

Other Clinic Birthing Statistics

Twins:

- Multiple sets delivered

Breech:

- External version, then delivery
- Vaginal Breech, incl primips

Fetal & neononatal death rate similar to in-hospital births

Interface of Birthing Program and Genetics

Mothers with disorders

- Sitosterolemia
- Hypertrophic cardiomyopathy
- Propionic Acidemia

Hx (risk) of affected babies

- Recessive disorders (Troyers, Galloway Mowat, BRAT1)
- Dominant – HCM; VWD
- X-linked – Hemophilia

Parental Screening

- Carrier Testing for individual disease (MSUD; sitosterolemia)
- Carrier Panels (future)

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Genetic Disorders in the Amish and Mennonite Populations

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Founder population

- Small number of individuals form a new community for reasons of ethnicity, religion, or geography
- Marriage occurs within their community
- Decrease in genetic variation occurs
- Some conditions absent; others may magnify in frequency

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Founder populations

- >1000 founder populations (700 in India alone)
- Amish & Mennonites are distinct founder populations
- Lessons learned are applicable to populations across the world
  - Specific diseases
  - Approach to diagnosis

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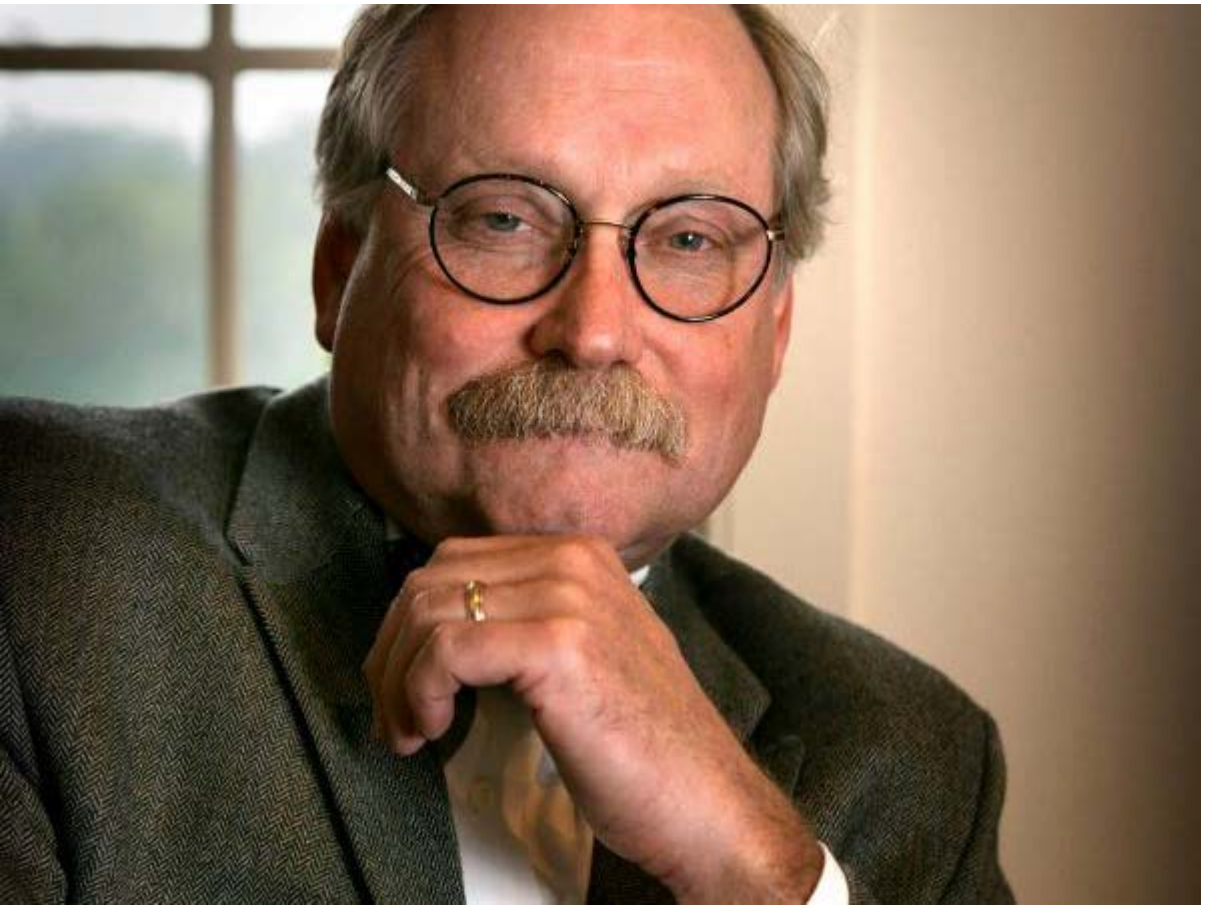
Father of study of inherited disorders in the plain population



Holmes Morton, MD
Clinic for Special Children

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Deep study of disorders in a specific population

Leads to

- Pattern recognition (& institutional knowledge)
- Low cost & efficient diagnosis
- Targeted variant development (TVARs) - $50
- Lists of known diagnoses in a population become possible

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Pathogenic Alleles Table

	A	B	C	D	E	F	G	H	I	J	K	L
1	Table2. Pathogenic Alleles Among the	Patients	Patients	Patients	CHC	Diagnosis	Gene symbol	Sequence variant	Protein variant	Population	Treatability	
2	Plain Populations of Pennsylvania, Eastern	CSC	OOC	BBPMC	Diseases	Holmes						
3	Maryland, Northeastern Ohio, Indiana,		Clinic		Amish &	County						
4	and the Midwest				Mennonites	WHGIC						
5					IN & MW							
6												
7	Disease TITLE											
8												
9	11-beta-hydroxylase deficiency	x					CYP11B1	c.1343G>A	Arg448His	Amish	1	
10	21 hydroxylase deficiency					1						
11	3-ß-OH-steroid dehydrogenase deficiency	x					HSD3B2	c.35G>A	Gly11Glu	Amish	1	
12	aldosterone deficiency	x					CYP11B2	5 bp deletion		Amish	1	
13	Alagille syndrome		x									
14	Amish albinism		x									
15	Amish [illegible]											
16	Brit[illegible]											
17	Auri[illegible]											
18	Bart[illegible]											
19	Beal[illegible]											
20	biot[illegible]											
21	biot[illegible]											
22	biot[illegible]											
23	Byle[illegible]											
24	Celu[illegible]											
25	Celi[illegible]											
26	Chai[illegible]											
27	chro[illegible]											
28	Cohe[illegible]											
29	Con[illegible]											
30	congenital hearing loss				x							
31	Congenital hypotonia					2						
32	congenital nephrotic syndrome	x					NPHS1	c.1481delC		Mennonite	1	
33	congenital nephrotic syndrome	x					NPHS1	c.3250delG		Mennonite	1	
34	Crigler-Najjar syndrome	x	x		x		UGT1A1	c.222C>A	Tyr74Ter	Amish and Me	1	
35	factor 11 deficiency	x					F11	c.1327C>T	Arg443Cys	Mennonite	1	
36	cleft palate				x							
37	familial cleft lip w/ or w/o cleft palate (?)		x									
38	familial craniosynostosis (?)		x									
39	non-syndromic deafness	x					GJB2	c.35delG		Mennonite	1	
40	familial deafness (?)		x									
41	familial hypercholanemia	x					TJP2	c.143T>C	Val48Ala	Amish	1	
42	familial hypercholanemia	x					BAAT	c.226A>G	Met76Val	Amish	1	
43	familial hyperlipidemia			10								
44	familial seizure w/ mental retardation		x									
45	familial seizure			3								
46	***fructose intolerance***		x									
47	galactosemia	x			x		GALT	c.563A>G	Gln188Arg	Amish	1	
48	***Gaucher disease***		x									
49	glucose/galactose malabsorption		x									
50	Gitelman syndrome	x					SLC12A3	c.1924C>G	Arg642Gly	Amish	1	
51	Gitelman syndrome	x					SLC12A3	8,627 bp deletion		Amish	1	
52	Gitelmans syndrome (? Different variant?)			7								
53	glutaric aciduria, type 1	x			x		GCDH	c.1262C>T	Ala421Val	Amish	1	

Consequences of a known diagnosis

- Cascade testing
- Carrier testing for sibs and other relatives
- Cord blood testing at birth

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Cord blood testing & early identification

Leads to

- Early effective treatment when known
- Opportunities for testing interventions early in life
- Avoidance of diagnostic odysseys
- Prompt transition to palliative care for lethal disorders

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Center for Special Children

- “Clinic within a clinic”
- Manage all family members & all ages
- Birthing center
- Board includes ½ or more members from plain community (president of Board is from plain community)

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Disorders

Metabolic disorders
- Propionic Acidemia
- Maple Syrup Urine Disease
- PKU
- Cobalamin C deficiency

Neurodevelopment disorders (severe)
- Galloway Mowat syndrome
- SNIP1
- Aicardi-Goutieres syndrome
- CNPNAP2 (caspr2)
- GM3 synthase deficiency
- BRAT1
- Pontocerebellar Hypolplasia

Neurodevelopmental syndromes (less severe)
- Troyer syndrome
- Ataxia-telangiectasia-like disorder type 2
- Amish brittle hair syndrome
- 16p11.2 duplication/deletion

Cardiovascular
- Sitosterolemia
- Hypertrophic cardiomyopathy
- Long QT2

Ocular disorders
- Oculocutaneous albinism
- Jalili syndrome
- Retinitis pigmentosa

Congenital hearing loss
- Connexin 26 (GJB2)
- SLITRK6

Respiratory/Immunologic
- Cystic Fibrosis
- Primary ciliary dyskinesia
- Cartilage hair hypoplasia
- RAG1 SCID
- DiGeorge syndrome

Miscellaneous
- Mucolipidosis (I cell disease)
- Corticosterone Methyloxidase 1 deficiency
- DGAT1 (protein losing enteropathy)

Sporadic (not founder) mutations
- Coffin Lowrey syndrome
- Williams syndrome
- Rett syndrome
- Neurofibromatosis
- Mandibulofacial dysostosis with microcephaly
- Sturge Weber syndrome
- CHD4
- GATA3
- Smith-Magenis
- ADNP/SYNGAP1

Novel Disorders
- CHD & ocular disease
- Developmental disability w/ SNHL

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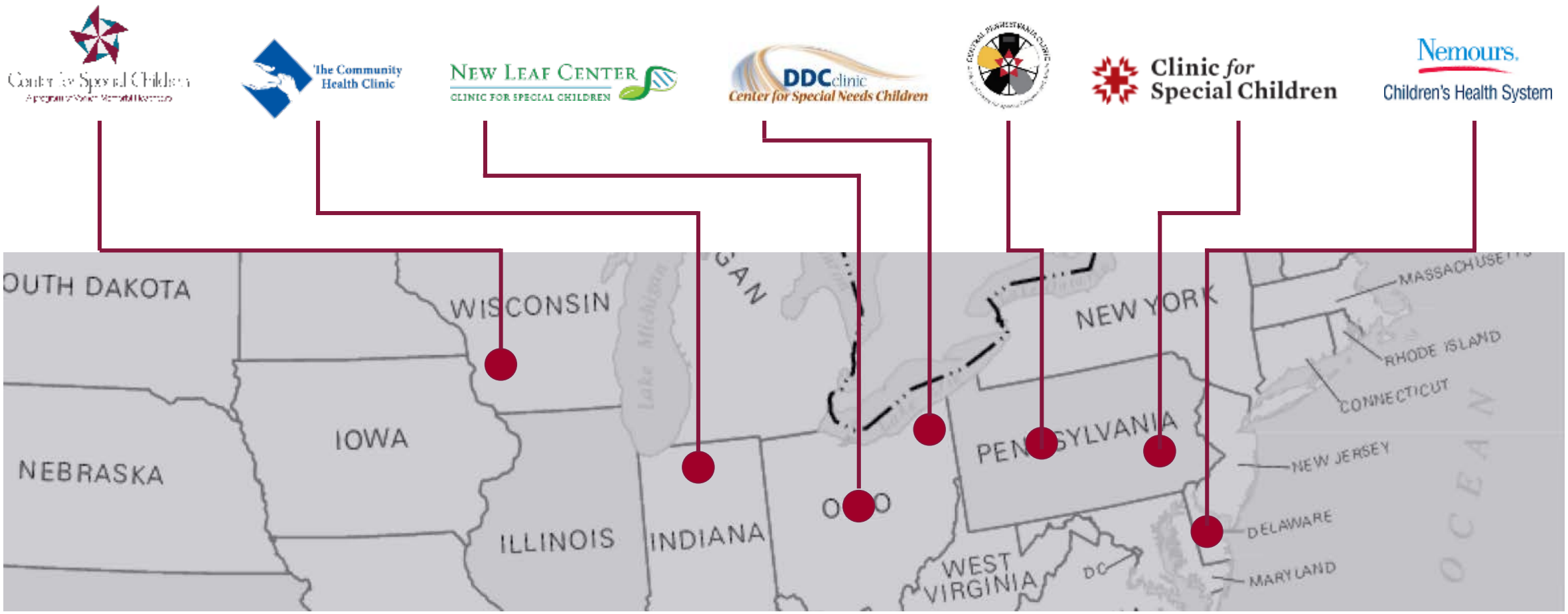
Plain Community Health Consortium



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Sitosterolemia (phytosterolemia)

- Disorder of plant sterol metabolism leading to dramatic elevation in levels, esp. sitosterol and campesterol
- Accelerated atherogenesis
- Hematologic effects
- ~ 100 reported cases
- Seen in Amish, Hutterites, Chinese, Korean, Middle East

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Sitosterolemia (phytosterolemia)

- Mutation in gene ABCG5 or ABCG 8
- Many mutations result in same phenotype
- Amish founder mutation (ABCG8 c.1720G>A)
- Sterol levels 50 to 200X normal

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Clinical features

- Accelerated atherogenesis (& aortic valve disease)
- Xanthomata (1/3 cases)
- Hematologic (hemolytic anemia; large platelets); bleeding risk?
- Orthopedic (lower extremity arthritis; Achilles' tendonitis)
- GI distress & poor growth (in subset)

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Treatment

- Ezetimibe
- Bile acid sequestrants
- Low sterol diet (limit veg. oils etc)
- Statins ineffective
- Stanols?

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What have we learned about sitosterolemia?

CIMT to study state of vasculature?

A work in progress

Fasting for sterol levels

	Before Meal	After Meal
Patient 1	61	55
Patient 2	67	63
Patient 3	81	82
Patient 4	56	54
Patient 5	59	55
Patient 6	59	63
Patient 7	34	35
Average	**60**	**58**

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Impact on Wound Healing

- 54 y/o man with penetrating injury to neck, involving esophagus
- Surgical intervention X5 (G-tube for months)
- Chronic open draining wound X 30 years
- After sitosterolemia Dx made, & treatment for one yr,
- Draining wound has healed and remains so

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What about stanol supplementation?

Atherosclerosis 227 (2013) 414–419

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Effects of plant sterol- or stanol-enriched margarine on fasting plasma oxyphytosterol concentrations in healthy subjects

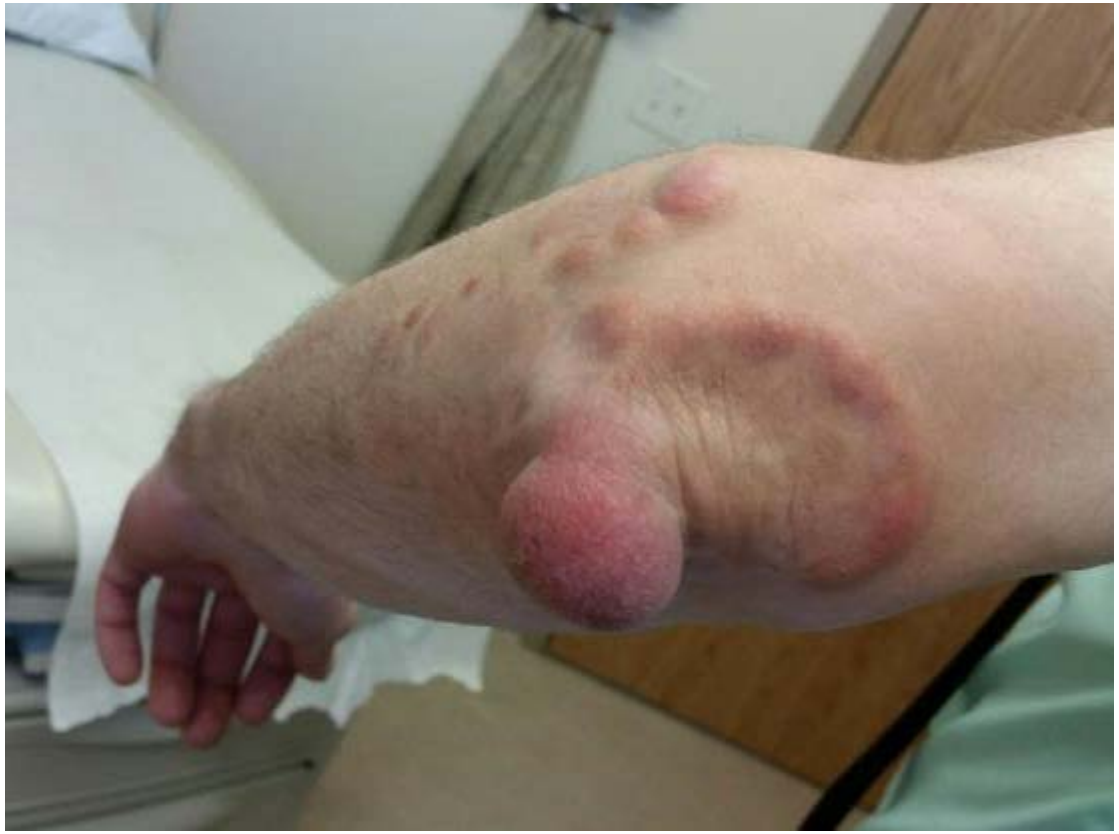
Sabine Baumgartner[a], Ronald P. Mensink[a], Constanze Husche[b], Dieter Lütjohann[b], Jogchum Plat[a,*]

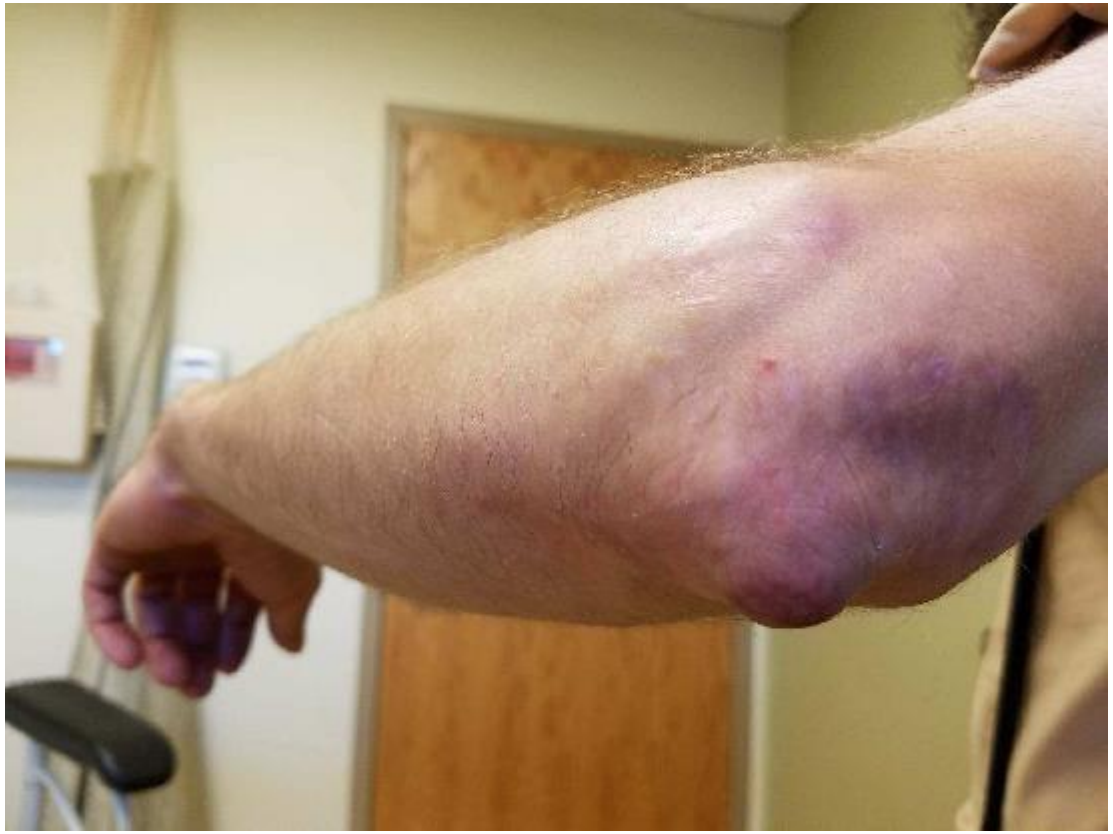
[a] Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands
[b] Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany

Effect of consumption of plant sterol and plant stanol-enriched margarines on serum lipid and lipoprotein concentrations, and on serum plant sterol, plant stanol and lathosterol levels.

	Control condition	Plant sterol condition	Plant stanol condition
Total cholesterol (mmol/L)	5.56 ± 1.07	5.26 ± 1.08[1]	5.27 ± 1.11[1]
LDL cholesterol (mmol/L)	3.36 ± 1.06	3.08 ± 1.00[1]	3.10 ± 1.05[1]
HDL cholesterol (mmol/L)	1.69 ± 0.39	1.65 ± 0.39	1.68 ± 0.39
Total cholesterol/HDL	3.46 ± 1.00	3.32 ± 0.93[2]	3.28 ± 0.96[3]
Triacylglycerol (mmol/L)	1.14 ± 0.40	1.18 ± 0.44	1.08 ± 0.41
ApoB100 (g/L)	0.97 ± 0.25	0.93 ± 0.24[3]	0.92 ± 0.26[3]
ApoA1 (g/L)	1.57 ± 0.31	1.55 ± 0.31	1.55 ± 0.27
Sitosterol*	140 ± 69	226 ± 255[3]	88 ± 35[4]
Campesterol	214 ± 83	346 ± 172[1]	131 ± 59[1,4]
Sitostanol	4.3 ± 3.3	5.5 ± 5.7	22.4 ± 11.7[1,4]
Campestanol	2.8 ± 1.6	3.5 ± 2.0	13.1 ± 7.7[1,4]
Lathosterol	115 ± 57	134 ± 56[3]	130 ± 55[2]
Cholestanol	165 ± 0.33	153 ± 32[2]	155 ± 32[2]

Xanthomata, before and after treatment





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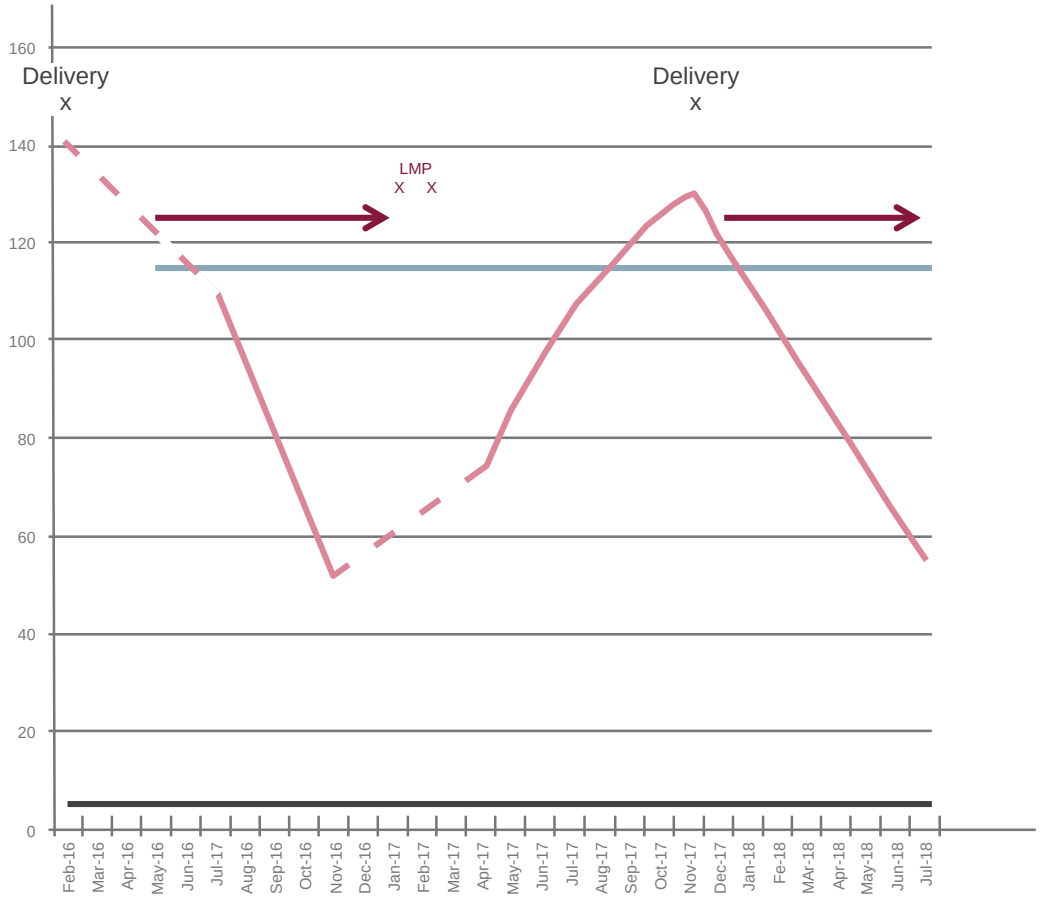
Management of sterols during pregnancy



Normal Sitosterol

Ezetimibe

Sitosterol Level

Cholestryramine Level

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Bleeding risk

- Platelet function studies normal
- Reassuring family history from two adult women (18 pregnancies – no transfusions, transfer to hospital, etc)
- Personal experience in two deliveries

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Other Studies in Pregnancy

- Fetal doppler flow studies (2nd trimester)– normal
- Platelet function studies - normal
- Placental pathology - a window to the microvasculature?
- 2 deliveries (one patient) - normal

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The Future in Genetic Assessment

Panels: For diagnosis
For couple screening

Clinic for Special Children

- >1000 mutations
- $490 (goal pricing: $100-$200)

DDC Clinic

- 125 disorders
- $400 (goal pricing: $100-$200)

UW-Madison (from filter paper)

- 100+ mutations
- Goal: $100

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Questions?

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