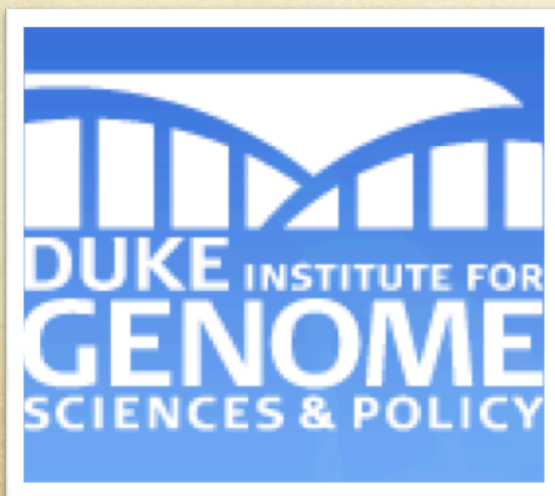


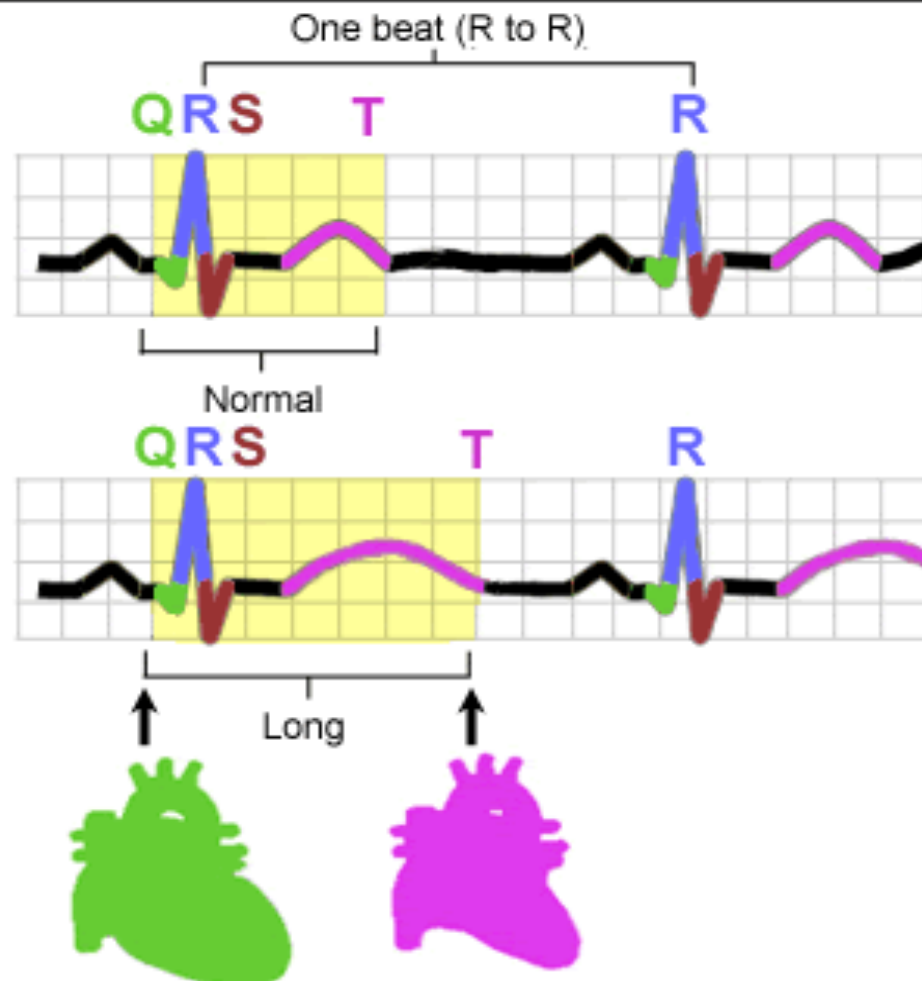
What Becomes of the Broken-Hearted: Gene Patents and Long QT Syndrome

Misha Angrist, PhD
Genomic and Personalized Medicine Forum
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Long QT Syndrome

Each section of an electrocardiogram (ECG or EKG) is referred to by a letter name: Q, R, S, and T.



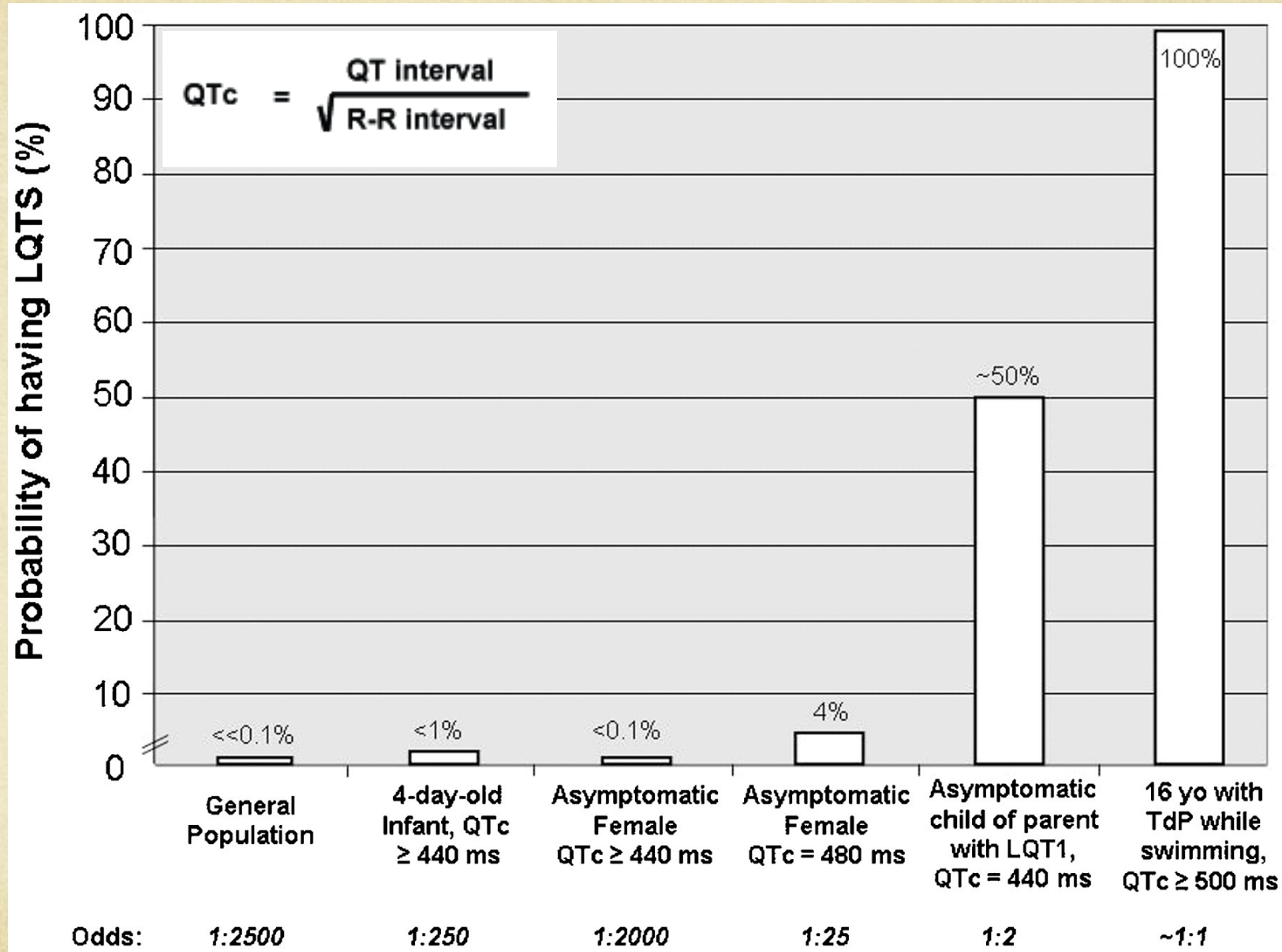


TABLE 1. LQTS Clinical Probability Score Card (ie, "Schwartz Score")

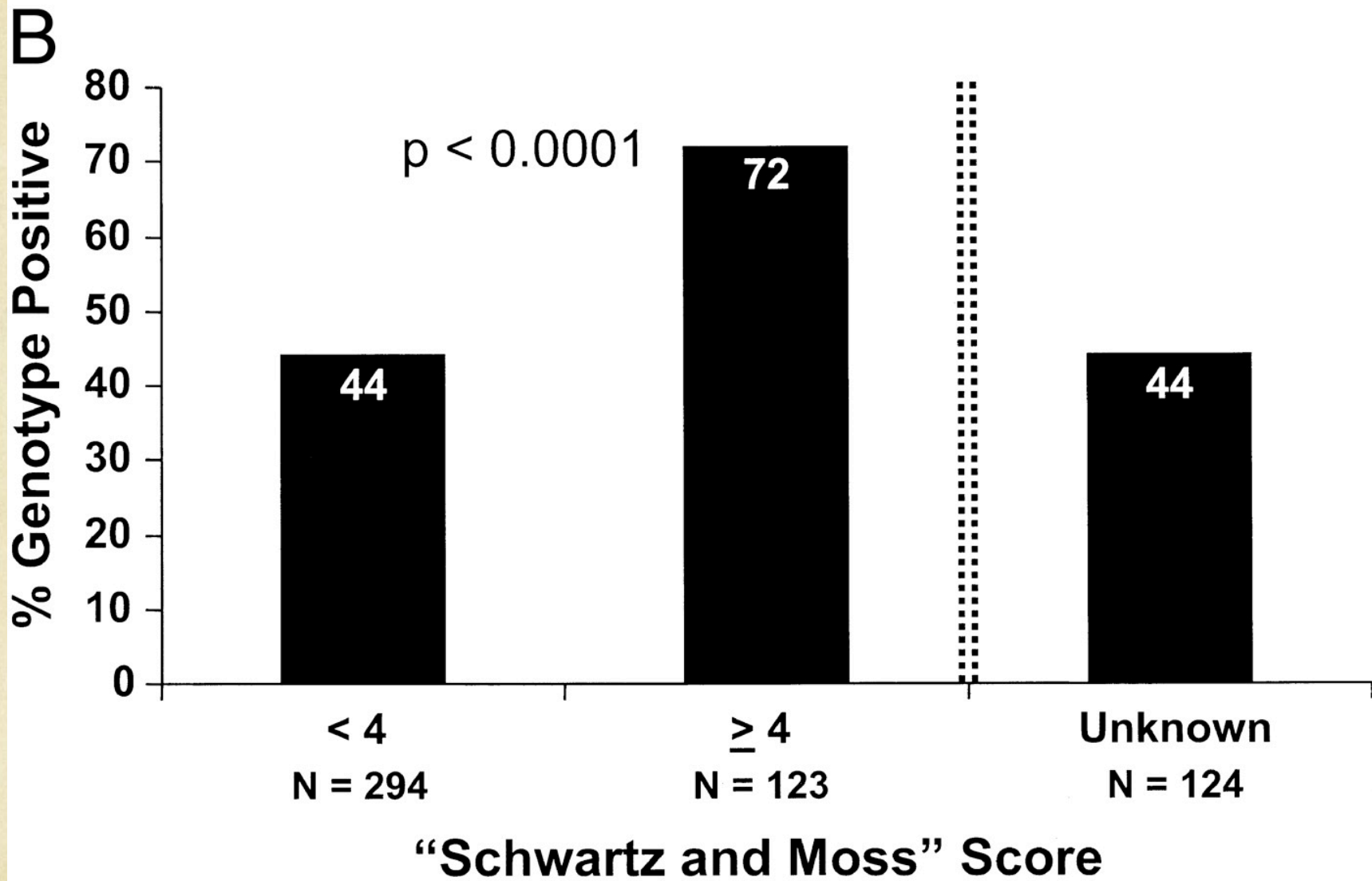
Finding	Points
History	
Clinical history of syncope*	
Without stress	1
With stress	2
Congenital deafness	0.5
Family history of LQTS†	1
Unexplained sudden death in a first-degree family member <30 y old†	0.5
ECG	
Corrected QT interval (QTc by Bazett's formula)	
450 ms (in males)	1
460–470 ms	2
>480 ms	3
Torsade de pointes*	2
T-wave alternans	1
>3 Leads with notched T waves	1
Bradycardia (<second percentile for age)	0.5

A score <1=low probability; 1 to <4=intermediate probability; ≥4=high probability.

*Syncope and torsade de pointes are mutually exclusive.

†Cannot count the same family member for both criteria.

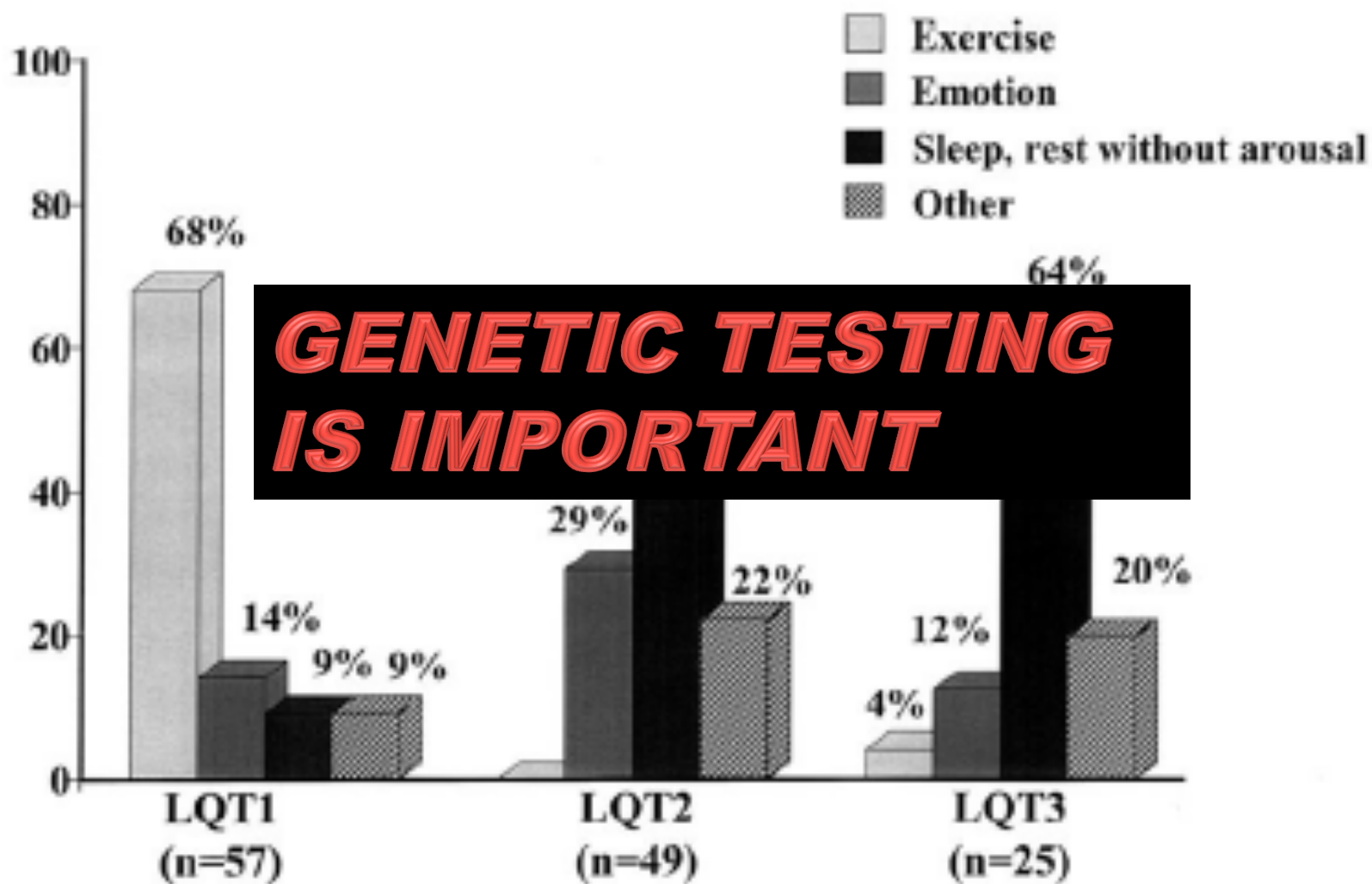
Adapted from Schwartz et al⁵ with permission from the American Heart Association. Copyright 1993.



Long QT Syndrome

- 1 in 3000 newborns
- Small but significant fraction of SCD in young people.
- β -blockers and ICDs are the most common therapies.
- Mutations in 12 susceptibility genes account for some 75% of familial LQTS
- Of that 75%, mutations in three genes account for the vast majority ($\approx 70\%$) of cases.

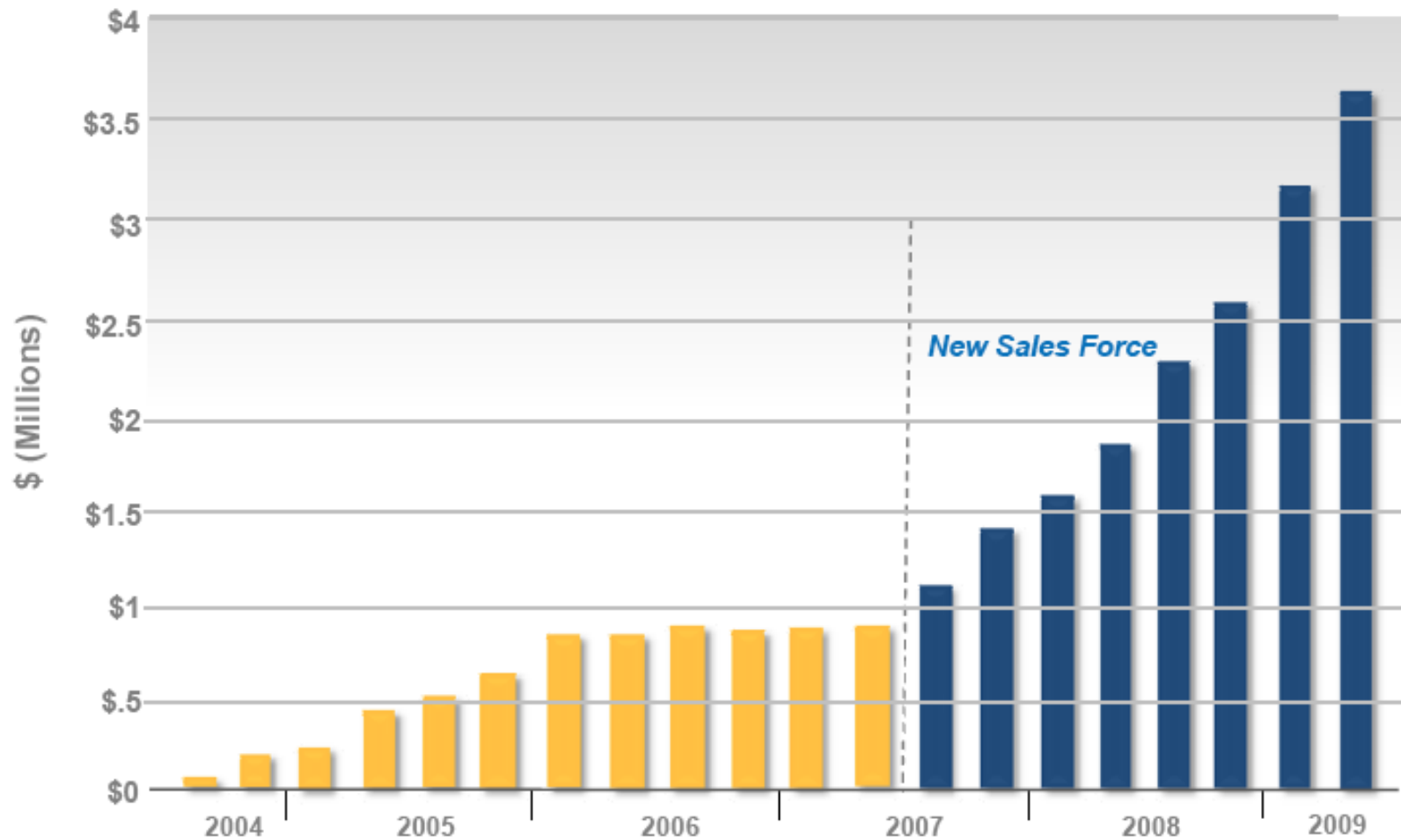
Triggers for lethal Events in the 3 main LQTS Genotypes



LQTS IP Chain of custody

- Initial LQTS genes discovered in 1990s by Mark Keating at University of Utah...NIH-funded
- First patent awarded in 1997
- DNA Sciences: sole licensee 1999-2003
- DNAS threatens legal action against labs: 2001-2002
- Genaissance Pharma purchases DNAS assets: 2003
- Genaissance launches 5-gene FAMILION test: 2004
- Clinical Data acquires Genaissance; PGxHealth subsidiary administers FAMILION from 2005

Dx for Inherited Cardiac Conditions: *FAMILION*[®]



Over 100% Growth Year Over Year*

20 *Calendar Year

CLINICAL DATA[®]

The Clinical Data/PGxHealth Era

- ❑ Test cost: \$5400 per proband; \$900 for confirmatory testing
- ❑ Reimbursement: Medicare; Medicaid in 41 states; total coverage now 280 million lives
- ❑ October 2007: Congressional hearings include a would-be competitor (Bio-Reference Laboratories) and a clinical geneticist. They criticize Clinical Data and report discrepancies in test results.
- ❑ Duke Center for Public Genomics asked by SACGHS to investigate

What we found in 2008

- There was a period from late 2002-2004 when enforcement actions by DNAS/GNSC kept existing commercial tests off the market
- The 2002 test covered fewer mutations
- Research labs have long turnarounds
- No prenatal diagnosis
- CLIA proficiency testing carried out by single, reputable research physician...and paid consultant to PGxHealth
- Limited peer-reviewed publications; private mutation database

Hello, Heisenberg?

- 2008: PGxHealth announces it will make its mutation data public
- 2009-2010: PGxHealth/Mayo scientists publish 3 peer-reviewed channelopathy mutation compendium papers; more than in previous 5 years
- 2010: Clinical Data includes extensive, 3-page list of IP holdings in 10-K

An international compendium of mutations in the *SCN5A*-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing

Jamie D. Kapplinger, BA,* David J. Tester, BS,* Marielle Alders, PhD,[†] Begoña Benito, MD,[‡] Myriam Berthet, BA,^{§||} Josep Brugada, MD, PhD,[¶] Pedro Brugada, MD, PhD,[#]

Genetic Testing for Long-QT Syndrome

Distinguishing Pathogenic Mutations From Benign Variants

Suraj Kapa, MD^{*}; David J. Tester, BS^{*}; Benjamin A. Salisbury, PhD^{*}; Carole Harris-Kerr, PhD[†]; Arthur A. M. Wilde, MD, PhD[‡]; Michael J. Ackerman, MD, PhD[§]

Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION[®] long QT syndrome genetic test

Jamie D. Kapplinger, BA,* David J. Tester, BS,* Benjamin A. Salisbury, PhD,[†] Janet L. Carr, PhD,[†] Carole Harris-Kerr, PhD,[†] Guido D. Pollevick, PhD,[†] Arthur A. M. Wilde, MD, PhD,[‡] Michael J. Ackerman, MD, PhD^{*}

A Patent Pas de Deux

- 2006: Bio-Reference Labs begins to amass LQTS IP left fallow by Clinical Data and previous patent holders
- 2009: Bio-Reference Labs/GeneDx launches its own LQTS test panel, screening for ten genes
- 2009: Clinical Data/PGxHealth ups *its* test to ten genes
- 2010: GeneDx screens all 12 genes; PGx screens 11
- 2010: GeneDx charges \$2500 out-of-pocket; PGx still charges \$5400 out-of-pocket

Closing Thoughts

- Wherever there has been an exclusive licensee in genetic dx, another company has been 1st to market
- Sunshine has been a good disinfectant, but not a panacea
- In LQTS, reimbursement has usually not been a problem
- CLIA is a fig leaf: regulators need to address COI issues in proficiency testing
- Without transparency, it's easier to game the system. BRLI exploited this to a positive outcome, but this was a function of luck, Utah's fecklessness...and a very savvy patent lawyer
- LQTS is rife with VUS. The inability to interpret genes is not limited to consumer genomics companies. Are we getting our money's worth?
- The Myriad case will likely have profound implications

Acknowledgments

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- Chris Heaney
- Jim Evans (UNC) and SACGHS
- The NIH ELSI program
- The LQTS community