One Community's Effort to Control Genetic Disease

| Kevin A. Strauss, MD, Erik G. Puffenberger, PhD, and D. Holmes Morton, MD

In 1989, we established a small community health clinic to provide care for uninsured Amish and Mennonite children with genetic disorders. Over 20 years, we have used publicly available molecular data and sophisticated technologies to improve diagnostic efficiency, control laboratory costs, reduce hospitalizations, and prevent major neurological impairments within a rural underserved community. These actions allowed the clinic's 2010 operating budget of $1.5 million to save local communities an estimated $20 to $25 million in aggregate medical costs. This exposes an unsettling fact: our failure to improve the lot of most people stricken with genetic disease is no longer a matter of scientific ignorance or prohibitive costs but of choices we make about how to implement existing knowledge and resources. (*Am J Public Health*. Published online ahead of print May 17, 2012:e1-e7. doi:10.2105/AJPH.2011.300569)

KEY FINDINGS

- Successful integration of molecular technologies into primary care can improve diagnostic efficiency, control laboratory costs, reduce hospitalizations, and prevent catastrophic clinical outcomes.
- Population-specific genetic information is a strong foundation for regional preventative health services. New high-density, low-cost genotyping methods afford the opportunity to actuate this model of care in small underserved communities throughout the world.
- Scaling molecular studies to small populations and even individual families is a reasonable scientific alternative to large scale genome wide association studies, and may help solve some intractable problems in human disease research and public health.

"I have no doubt that it is possible to give a new direction to technological development, a direction that shall lead it back to the real needs of man."
E.F. Schumacher, 1974[1]

"Stunning scientific and technological advances in genetics will mean little if they do not benefit people."
A. Guttmacher et al., 2001[2]

GENES AND PEOPLE

A decade after completion of the Human Genome Project,[3-5] its effect on medical practice has fallen short of expectations.[6-8] The United States commands 35% of the worldwide public budget for the study of genomics,[9] but less than 3% funds research directly concerned with the treatment of genetic disease in humans[10]—the kind of research, as Goldstein and Brown[11] surmised, that requires the "investigator to shake hands with the patient." The bulk of public investment supports large-scale genome-wide association studies,[12-16] experiments on cells and model organisms,[17] and efforts to patent genes.[18]

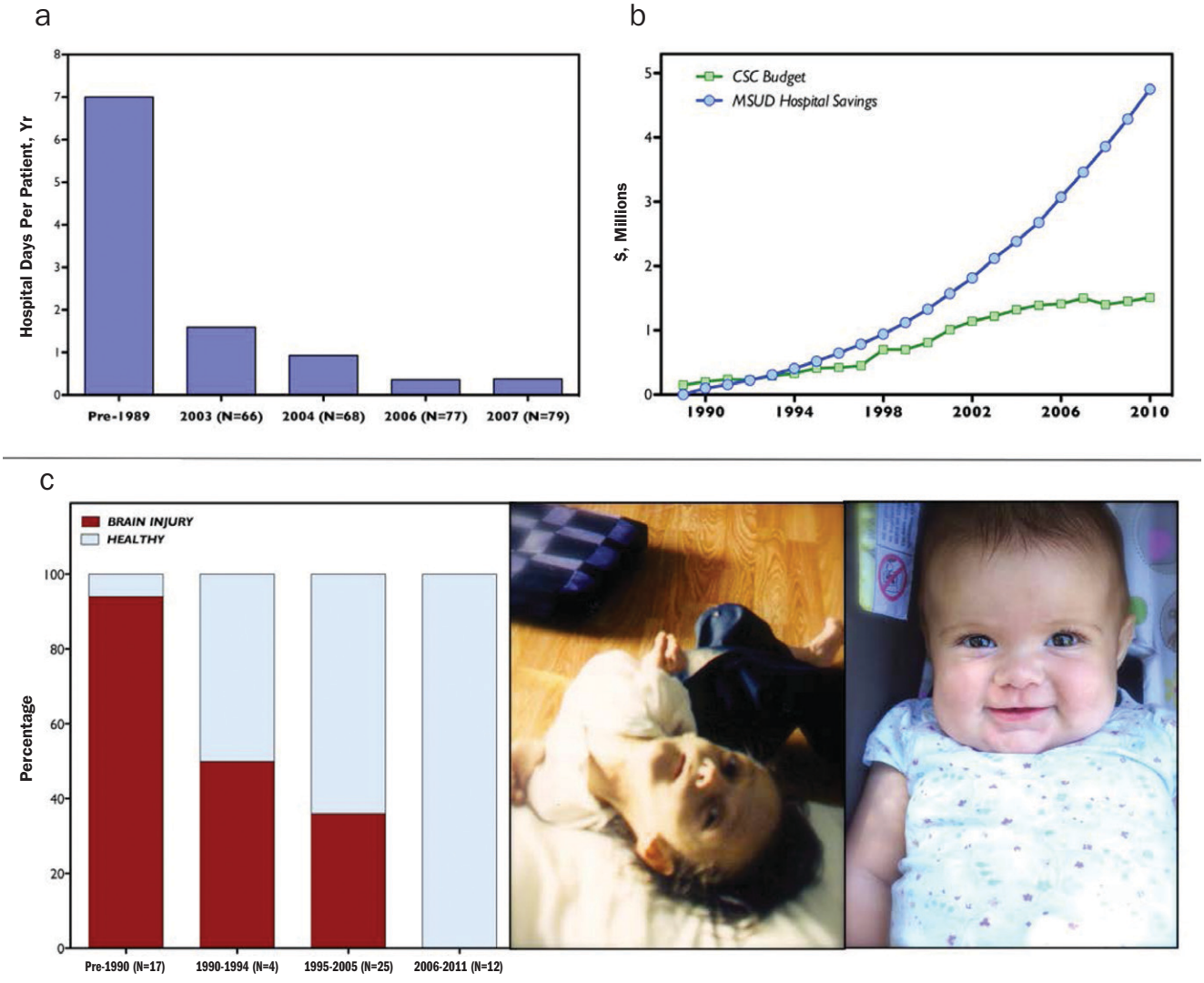
We have tried to keep progress in genomic science firmly rooted in the everyday needs of vulnerable people.[2,4,19] Our Clinic for Special Children was established 20 years ago to incorporate subspecialty knowledge of population genetics, molecular biology, and the technologies these entail into a rural pediatric clinic serving uninsured Amish and Mennonite (Plain) children with genetic disease.[20,21] It was built in a Pennsylvania cornfield, amid a large Plain settlement, to export practical expertise to where it was needed (see box on page e3).[20,22] Our work was guided by a simple concept: the best chance to prevent the catastrophic effects of any gene mutation is to focus on early diagnosis—to start with a healthy child—and provide longitudinal follow-up care that seamlessly integrates subspecialty knowledge into general practice.[20,22,23]

THE GROWTH OF COMMUNITY GENETICS

Early work at the clinic focused on a few volatile conditions such as glutaric acidemia type 1 and maple syrup urine disease,[24,25] which affect about 1 per 400

Amish and Mennonite infants (see the box on page e4). In the first year of operation, we developed systematic laboratory methods and clinical protocols to treat metabolic disorders locally.[25] These services decreased hospitalizations and neurological injuries, which quickly drove down the cost of care (Figure 1). Building on early successes with maple syrup urine disease and glutaric acidemia type 1,[25-27] clinic activities expanded to address a much broader scope of community health needs, such as immunization, midwife education, neonatal vitamin K prophylaxis, mutation carrier testing, and newborn screening.

Over time, it became apparent that most genetic disorders present to generalists as common problems such as failure to thrive, cerebral palsy, epilepsy, anemia, and sepsis.[22,28,29] By the late 1990s, we saw how primary care could be transformed by the Human Genome Project and its attendant technologies[5] and, in 1998, hired a molecular biologist to work alongside clinic doctors. At the time, this seemed



Note. MSUD = maple syrup urine disease. Over the last 20 years, we have introduced changes in outpatient monitoring and treatment that decreased (MSUD hospitalizations from 7.0–0.4 days per patient per year. This 94% decrease in hospital costs applied to 81 maple syrup urine disease patients under our care saves the community at least $4.3 million annually—nearly 3 times the clinic's operating budget (a, b). The first genetic study at the clinic identified glutaric acidemia type 1 as the cause of "Amish cerebral palsy." Beginning in 1989, the clinic offered on-site diagnostic screening, comprehensive pediatric follow-up care, and inpatient treatment at the local community hospital. Brain injuries causing severe dystonia (c, middle panel) decreased from 94% to 36% by 1995 (c, left panel). Since the introduction of a new glutaric acidemia type 1 lysine-free, arginine-rich medical formula, designed by clinic doctors in 2006, there have been no brain injuries among 15 consecutive glutaric acidemia type 1 patients over 28 aggregate patient-years (c, right panel).

FIGURE 1—MSUD-related (a) hospitalization days, (b) hospital costs, and (c) as well as glutaric acidemia-related brain injuries during the last 20 years: Clinic for Special Children, Strasburg, PA.

TABLE 1—Comparison of Price and Turnaround Time for Laboratory Services: Clinic for Special Children, Strasburg, PA.

	Commercial Laboratory[a]		University Laboratory[b]		Clinic for Special Children Laboratory				
	Cost, US $	Turnaround, Days	Cost, US $	Turnaround Days	Cost, US $	Turnaround	No. per Year	Savings, US $	Patient-Days Saved Yearly
Amino acid analysis	700	5	240	4	75	45 min	1310	517 450	5856
Organic acid analysis	247	6	230	6	85	4 h	175	26 863	1024
Targeted detection of known mutation[c]	590	14	225	21	50	1–2 d	405	144 788	6480
Complete gene sequencing, cost per exon[d]	147	11	148	28	35	5 d	15	1688	218
Cytogenetic microarray (DNA copy number)	1654	21	1550	28	600	4 d	145[e]	222 290	2973
Totals								913 078	16 549

[a]http://www.mayomedicallaboratories.com/test-catalog.
[b]http://www.bcm.edu/geneticlabs.
[c]For commercial and university laboratories, the cost of mutation detection varies; prices listed are averages. At the Clinic for Special Children, the cost of detecting any mutation is the same, regardless of the method used (e.g., gene sequencing, real-time polymerase chain reaction, light scanner).
[d]Costs represent averages from 9 genes ranging in size from 4 to 27 exons (range = $73–$253 per exon).
[e]50 microarrays were performed for clinical copy number analysis, 95 were used for research (e.g., gene mapping).

THE CLINIC FOR SPECIAL CHILDREN, STRASBURG, PA

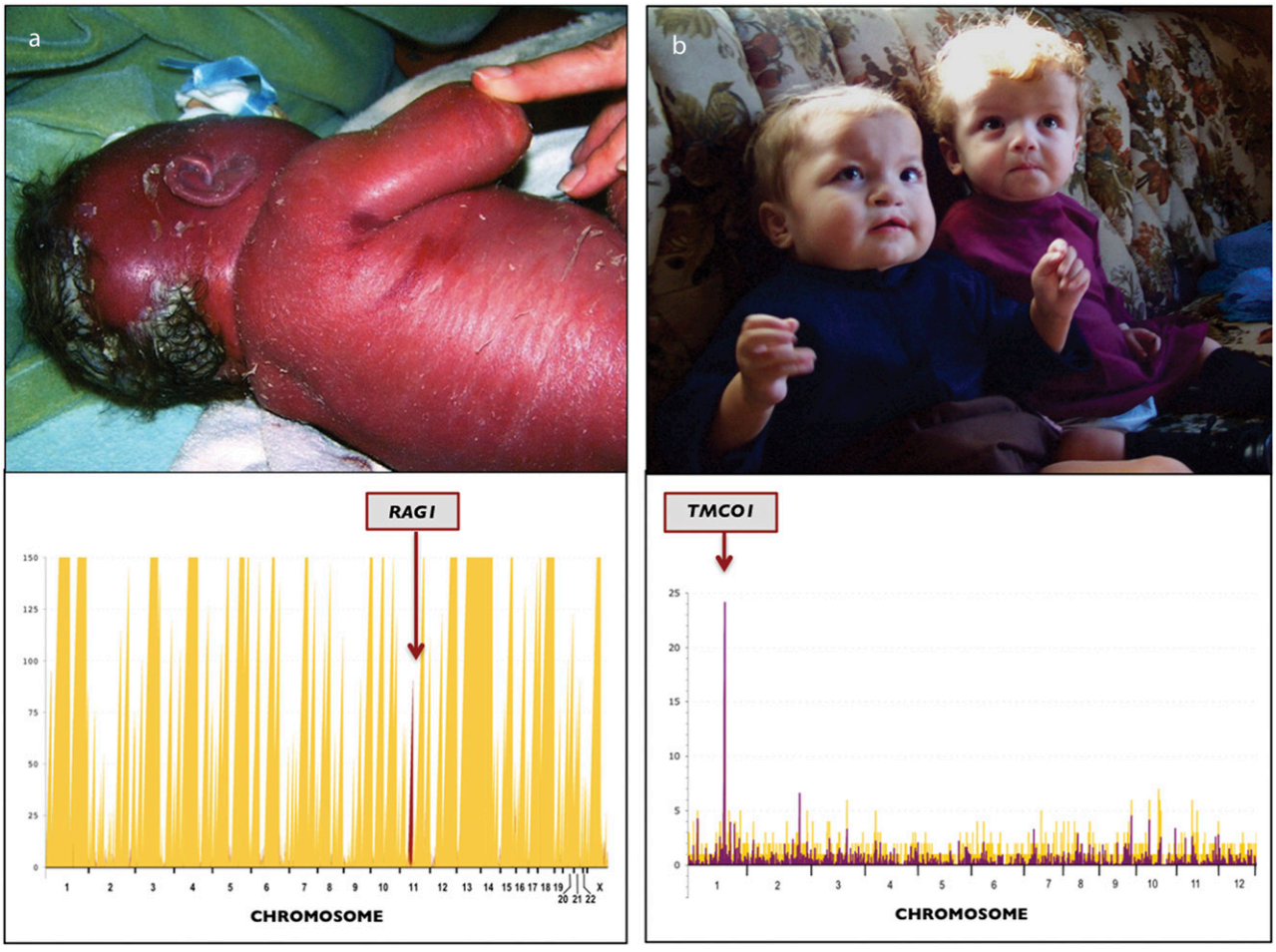
The Old Order Amish and Mennonite (Plain) populations of Pennsylvania are descended from Swiss Anabaptist immigrants who came to the New World in the early 18th century fleeing 2 centuries of violent religious persecution. They dispersed into many small endogamous farming settlements throughout North America and have eschewed modern ways, including medical insurance. Their health risks are deeply rooted in this history: population bottlenecks and genetic drift gave rise to a particular distribution of pathogenic alleles among North American settlements that have caused much individual and communal suffering over the last 2 centuries, compounded by poor access to the market-based US health care system.

In 1989, we established the nonprofit Clinic for Special Children (Figure A, available as a supplement to the online version of this article at http://www.ajph.org) to care for Plain children with genetic disorders. Fundamental aims of our practice were to identify the regional genetic causes of childhood disability and illness, use technologies in the field to diagnose and treat them, and make care accessible and affordable. The clinic gained support from local Anabaptist communities, who came to see it as a valuable investment in their children; they provided leadership and financial backing for a charitable regional health care initiative fundamentally different from the profit-driven US health care market. Of our patients, 95% are uninsured, and the clinic receives no state or federal money. In 2010, we spent $1.5 million providing comprehensive medical care for 1877 patients ($799 per patient) and offered on-site molecular testing for 103 different pathogenic alleles.

Fees cover one third of the budget. An additional third represents contributions by individual donors, many of whom choose to remain anonymous. One third of the budget is raised through 4 annual quilt auctions organized by the Plain people. The largest of these, celebrating its 20th anniversary in Leola, Pennsylvania, raised $310 000 in 9 hours through the sale of donated quilts, furniture, homemade food, and farm goods. By comparison, 2010 medical spending for the US population was $8344 per person, half of which was paid by state and federal governments and the remainder split about equally between patients and private insurers.

like an obvious way to harness the clinical potential of Human Genome Project databases. In retrospect, it proved a crucial innovation.

We built a Clinical Laboratory Improvement Amendment–certified core molecular laboratory, integral to the practice, which could be used to respond flexibly to the needs of individual patients and explore broader patterns of genetic risk within the population (Figure 2).[20] Over 2 decades, we sought ways to exploit emerging technologies for clinical aims and, by working on a small scale, kept operating costs low (Table 1).[30,31] By coupling population-based carrier testing and preemptive diagnoses to good local care, we have been able to limit morbidity,[27] contain medical costs,[31] and prevent serious neurological injury in more than 200 children (10% of our patients; Figure 1; see box on page e7).[26,32,33]



Note. The Amish girl born with alopecia, diffuse swelling, and thick inflamed skin nearly died of bacterial sepsis at age 3 weeks. We compared her homozygous DNA markers (lower panel, red peak) with overlaid homozygous peaks from 7 healthy siblings (yellow peaks) and identified 1 region on chromosome 11 where she had a unique stretch of DNA. This region contained the *RAG1* gene, which had a pathogenic c.2974A>G change. These same DNA markers were used to search for a suitable hematopoietic stem cell donor among her siblings and matched human leukocyte antigen (HLA) loci between the patient and her youngest sister. The child is alive and well 4 years after a stem cell transplant (a). The 2 Amish siblings had skeletal abnormalities and psychomotor delay. Their parents, uninsured farmers, spent >$20 000 on diagnostic testing at a regional children's hospital. At the clinic, a 10 000-marker DNA mapping study quickly localized the condition to the *TMCO1* gene on chromosome 1 for a total cost of <$1000. The clinic spends $35 000–$50 000 to map, identify, and develop carrier testing for 5–16 new pathogenic alleles each year. New technologies (e.g., microarrays, melting-curve analysis, exome sequencing), once available, are quickly put into clinical practice (b).

Source. Reprinted from Strauss et al.[31] Copyright 2008, with permission from Elsevier.

FIGURE 2—DNA mapping for (a) personalized genomic medicine for an Amish girl born with alopecia, diffuse swelling, and thick inflamed skin and (b) investigation of population genetic risks for 2 Amish siblings with skeletal abnormalities and psychomotor delay: Clinic for Special Children, Strasburg, PA.

MANY POPULATIONS, ONE BIOLOGY

Genetic bottlenecks exist within Arab and Israeli nations, Nordic countries, India and other parts of Asia, and certain African and Latin American subpopulations and among Native American, First Nations, and other indigenous peoples. Each of these populations will have a particular constellation of genetic disease risks, and understanding this diversity is key to effective public health initiatives. Genotyping projects focused on public health are already under way in Mexico, India, and Thailand. Among these diverse populations, genomics must be integrated into medical practice amid a dense matrix of regional economic details and clinical facts. Vague or indeterminate clinical information often limits the utility of large genome-wide association studies within the "general population." This problem arises naturally in a system that separates the people who make clinical observations and provide care from those who produce genetic data. In an important sense, this is the crux of the problem. The many levels of human organization—genetic structure, proximate environmental conditions, physiology, economics, and culture—are inseparable for the purpose of understanding and treating disease.

Regional or population-based initiatives to control genetic disease should inform the broader sweep of human genomics research. Over the last decade, our approach has attracted the attention of investigators elsewhere. Many collaborating clinicians and scientists are interested in how "small" science can inform fundamental problems in biology and guide "big" genomic science in clinically useful directions. The story of *CNTNAP2* provides one such example. In 2006, we collaborated with the Translational Genomics Research Institute (http://www.tgen.org/) to identify a homozygous 3709delG frameshift in exon 22 of *CNTNAP2* among a group of closely related Amish children who had complex partial epilepsy and autism. Subsequent studies identified *CNTNAP2* variants in non-Amish patients throughout the world who had diverse clinical presentations, including idiopathic autism, epilepsy, language disorders, and schizophrenia. These discoveries kindled research into the function of CNTNAP2 during human brain development and identified its role in frontal lobe connectivity and modulation of FOXP2, a critical protein in the evolution of language.

The study of many other Mendelian and "complex" diseases (e.g., depression, obesity, type 2 diabetes) will likely be enriched by focused regional studies. These common conditions arise from interactions among multiple gene variants in conjunction with epigenetic, environmental, and stochastic factors. The discovery of rare, highly penetrant alleles among small social groups may be the key to detecting their basic genetic foundations. We recently launched collaborative genetic studies of bipolar illness, attention-deficit disorder, and major depression in the Plain populations of Pennsylvania and have teamed up with the Broad Institute (http://www.broadinstitute.org) to determine how deep sequencing technologies can be effectively deployed in primary care settings.

GENETICS, ECONOMICS, AND PUBLIC HEALTH

We see no fundamental reason why this approach cannot be replicated in other settings (see box on page e5). The cost of genotyping is decreasing quickly, and industry will soon deliver the "$1000 genome," which costs less than many routine diagnostic tests and considerably less than a new wheelchair.[34] According to a recent guideline,[35] the standard diagnostic evaluation of a child with nonspecific global developmental delay costs between $10 000 and $20 000 (table available as a supplement to the online version of this article at http://www.ajph.org). Each year, we invest the equivalent of just 2 such workups—about $35 000—on molecular studies used to map and develop testing for 5 to 16 new pathogenic alleles. By adapting low-cost melting curve analysis ($50 per run, turnaround 4 hours)[32] to detect these conditions, we eliminate about $700 000 of unnecessary diagnostic testing annually.

Although genotyping services add to operational cost in a primary care setting, the cost of ignorance is steeper. Infants with undetected genetic disease do not vanish from the medical system; they go on to develop disability and chronic disease and require substantial medical resources. Overall cost saving depends on investing more in some services (e.g., molecular diagnostics and primary care infrastructure) to reduce the need for others (hospitalization and chronic care).

In Lancaster County, Pennsylvania, preemptive genomic medicine has a measurable effect on public health: among 110 genetic disorders managed at the clinic, 41% can now be treated

BUILDING A MEDICAL HOME

Before the Clinic for Special Children's inception, Plain children with maple syrup urine disease, glutaric acidemia type 1, and other complex genetic disorders had fragmented care that was costly and ineffective; parents were uneducated about home management, traveled 100 miles or more during medical emergencies, and paid cash for services at rates 3- to 4-fold standard Medicaid reimbursement. Childhood mortality from maple syrup urine disease was 39%, and 94% of Amish children with glutaric acidemia type 1 were fully disabled by metabolic strokes before age 2. Before 1989, Mennonites born with maple syrup urine disease arrived critically ill to regional pediatric centers where they stayed an average of 12 weeks. These hospitalizations cost $50 000 or more. Among the 61% of patients who survived childhood, most were moderately or severely disabled. Beyond infancy, each patient was hospitalized about once yearly for 7 days, which today would cost an average of $8000 per day (range = $1000–$38 000 per day).

Since 1989, we have managed Mennonite maple syrup urine disease in 68 patients longitudinally from the newborn period. Half of them were targeted because of a positive family history or carrier testing and diagnosed on site between 12 and 24 hours of life; all these children transitioned safely at home. The remainder were diagnosed by newborn screening and hospitalized for an average of 5 days.

The clinic developed affordable on-site amino acid testing, home well-day and sick-day protocols, and on-demand emergency parenteral solution so that Northeastern Mennonites born today with maple syrup urine disease can expect to grow up healthy (Figure B, available as a supplement to the online version of this article at http://www.ajph.org).

decisively. For an additional 36%, informed medical care allows children to suffer less and live more independently. Our operational spending of $1.5 million saves the Plain community between $20 and $25 million in aggregate medical costs each year (about $12 000 per patient per year). Allowing for some uncertainty in such estimates, the conclusion is straightforward: genomic science can be deployed in community settings to deliver better health care for less cost, but this requires balancing the science of discovery with a science of implementation.[36-38]

Systems of medical care that allow clinicians and molecular biologists to work side-by-side at the appropriate scale, concerned foremost with the care of patients,[39] are a means to ensure that affordable gene-based methods become a sustainable force in medical practice.[16,40-42] Critics who argue that social and cultural factors dictate what represents "appropriate technology" in any particular setting[43,44] should remember that persons born with serious genetic lesions are victims of chance and should have preferential claim to the practical benefits of scientific progress (http://www.un.org/en/documents/udhr).[36,38,43,45] ■

About the Authors

The authors are with Clinic for Special Children, Strasburg, PA, and the Department of Biology, Franklin and Marshall College, Lancaster, PA. Kevin A. Strauss and D. Holmes Morton are also with Lancaster General Hospital, Lancaster, PA.

Correspondence should be sent to Kevin A. Strauss, MD, Clinic for Special Children, 535 Bunker Hill Rd, Strasburg, PA 17579 (e-mail: kstrauss@clinicforspecialchildren.org). Reprints can be ordered at http://www.ajph.org by clicking on the "Reprints" link.

This article was accepted November 6, 2011.

Contributors

K.A. Strauss conceptualized the article, coauthored most of the text, and was primary author of figures, sidebars, and boxes. E.G. Puffenberger codesigned the article and compiled all molecular data therein, prepared Table 1 and panels for Figures 1 and 2, and contributed written text pertaining to core laboratory studies and population genetics. D. Holmes Morton helped conceptualize the article, coauthored boxes, contributed original text pertaining to public health/medical home, and provided key edits and oversight for the final revision.

Acknowledgments

The Clinic for Special Children is funded in part by charitable donations from the Amish and Mennonite communities of North America. Work by D. Holmes Morton is supported by an award from the John D. and Catherine T. MacArthur Foundation.

Human Participant Protection

Clinical and molecular research at the Clinic for Special Children is regularly reviewed by the institutional review board of Lancaster General Hospital and proceeds only with written informed consent of parents on behalf of their children; this article does not contain any original research but is a review of previously published institutional review board–approved studies. Parents consented in writing to publication of deidentified photographs of their children for use in this publication.

References

1. Schumacher EF. *Small Is Beautiful.* New York, NY: HarperCollins; 1974.

2. Guttmacher AE, Jenkins J, Uhlmann WR. Genomic medicine: who will practice it? A call to open arms. *Am J Med Genet.* 2001;106(3):216–222.

3. Lander ES, Linton LM, Birren B, et al; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature.* 2001;409(6822):860–921.

4. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA.* 2001;285(5):540–544.

5. McKusick VA. The anatomy of the human genome: a neo-Vesalian basis for medicine in the 21st century. *JAMA.* 2001;286(18):2289–2295.

6. Lander ES. Initial impact of the sequencing of the human genome. *Nature.* 2011;470(7333):187–197.

7. Zerhouni EA. Translational and clinical science—time for a new vision. *N Engl J Med.* 2005;353(15):1621–1623.

8. Dorn GW, Cresci S. Genome-wide association studies of coronary artery disease and heart failure: where are we going? *Pharmacogenomics.* 2009;10(2):213–223.

9. Pohlhaus JR, Cook-Deegan RM. Genomics research: world survey of public funding. *BMC Genomics.* 2008;9:472–490.

10. U.S. Department of Health & Human Services. Fiscal Year 2010 Budget in Brief: National Institutes of Health. 2010. Available at: http://dhhs.gov/asfr/ob/docbudget/2010budgetinbriefh.html. Accessed August 1, 2011.

11. Goldstein JL, Brown MS. The clinical investigator: bewitched, bothered, and bewildered—but still beloved. *J Clin Invest.* 1997;99(12):2803–2812.

12. Evans JP, Meslin EM, Marteau TM, Caulfield T. Genomics: deflating the genomic bubble. *Science.* 2011;331(6019):861–862.

13. Suarez-Gestal M, Perez-Pampin E, Calaza M, Gomez-Reino JJ, Gonzalez A. Lack of replication of genetic predictors for the rheumatoid arthritis response to anti-TNF treatments: a prospective case-only study. *Arthritis Res Ther.* 2010;12(2):R72.

14. Gamulin S. Impact of molecular medicine on pathophysiology, medical practice, and medical education. *Croat Med J.* 2003;44(4):374–385.

15. Doi K, Okamoto K, Tokunaga K, Fujita T, Noiri E. Genome study of kidney disease in the age of post genome-sequencing. *Endocr Metab Immune Disord Drug Targets.* 2008;8(3):173–183.

16. Khoury MJ, Bowen MS, Burke W, et al. Current priorities for public health practice in addressing the role of human genomics in improving

THE SCIENCE AND ECONOMICS OF PREVENTION

We observe firsthand why pediatric practice is such a vital place to gather and apply our growing knowledge of human genetics; here we can best leverage its preventive power. Like maple syrup urine disease and glutaric acidemia type 1, about half of the genetic disorders we manage can cause major disability, and many of these are treatable. The Clinic for Special Children invests heavily in research and methods aimed at detecting infants who are genetically at risk before they develop brain injury.

Few have attempted to place a dollar value on this type of strategy, but in 2004, the Centers for Disease Control and Prevention estimated lifetime costs, including costs attributable to medical care, assistive devices, transportation, special education, and lost productivity of disabled individuals and their caregivers, associated with the diagnoses of mental retardation, cerebral palsy, hearing loss, and visual impairment. Adjusted for a 6.1% medical inflation rate, they ranged from $630 000 (hearing loss) to $1 530 000 (mental retardation) per lifetime. These estimates indicate that preventing major neurological disability in approximately 200 children over the clinic's 20-year history has spared the Plain communities about $270 million in associated costs. The clinic's cumulative operating cost over this same period was $18.3 million.

An Amish boy with severe psychomotor delay and arrested brain growth (Figure C, available as a supplement to the online version of this article at http://www.ajph.org) remained without a diagnosis after an extensive workup at a tertiary center. We subsequently identified a homozygous mutation in the *MTHFR* gene (c.1129C>T), which encodes 5,10-methylene tetrahydrofolate reductase, and found a 30% carrier frequency for this allele within the Somerset County Amish settlement. In collaboration with the Pediatrix Screening Laboratory, we developed a real-time polymerase chain reaction method for detecting the *MTHFR* c.1129C>T allele in dried filter paper blood spots. The first child diagnosed by real-time polymerase chain reaction was the sister of the proband (right), started therapy her second week of life, and has had normal brain growth and development during 4 years of follow-up.

population health. *Am J Prev Med.* 2011;40(4):486–493.

17. Zaragoza C, Gomez-Guerrero C, Martin-Ventura JL, et al. Animal models of cardiovascular diseases. *J Biomed Biotechnol.* 2011;2011:497841.

18. Pressman L, Burgess R, Cook-Deegan RM, et al. The licensing of DNA patents by US academic institutions: an empirical survey. *Nat Biotechnol.* 2006;24(1):31–39.

19. Watson JD. *DNA: The Secret of Life.* New York, NY: Alfred A. Knopf; 2003.

20. Strauss KA, Puffenberger EG. Genetics, medicine, and the Plain people. *Annu Rev Genomics Hum Genet.* 2009;10:513–536.

21. Puffenberger EG. Genetic heritage of the Old Order Mennonites of southeastern Pennsylvania. *Am J Med Genet C Semin Med Genet.* 2003;121C(1): 18–31.

22. Morton DH, Morton CS, Strauss KA, et al. Pediatric medicine and the genetic disorders of the Amish and Mennonite people of Pennsylvania. *Am J Med Genet C Semin Med Genet.* 2003;121C(1):5–17.

23. Morton DH. Through my window—remarks at the 125th year celebration of Children's Hospital of Boston. *Pediatrics.* 1994;94(6 pt 1):785–791.

24. Morton DH, Bennett MJ, Seargeant LE, Nichter CA, Kelley RI. Glutaric aciduria type I: a common cause of episodic encephalopathy and spastic paralysis in the Amish of Lancaster County, Pennsylvania. *Am J Med Genet.* 1991;41(1):89–95.

25. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* 2002;109(6):999–1008.

26. Strauss KA, Brumbaugh J, Duffy A, et al. Safety, efficacy and physiological actions of a lysine-free, arginine-rich formula to treat glutaryl-CoA dehydrogenase deficiency: focus on cerebral amino acid influx. *Mol Genet Metab.* 2011;104(1-2):93–106.

27. Strauss KA, Wardley B, Robinson D, et al. Classical maple syrup urine disease and brain development: principles of management and formula design [published erratum appears in *Mol Genet Metab.* 2011;103(2):202]. *Mol Genet Metab.* 2010;99(4):333–345.

28. Puffenberger EG, Hu-Lince D, Parod JM, et al. Mapping of sudden infant death with dysgenesis of the testes syndrome (SIDDT) by a SNP genome scan and identification of TSPYL loss of function. *Proc Natl Acad Sci U S A.* 2004;101(32):11689–11694.

29. Strauss KA, Puffenberger EG, Huentelman MJ, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med.* 2006;354(13):1370–1377.

30. Strauss KA, Puffenberger EG, Craig DW, et al. Genome-wide SNP arrays as a diagnostic tool: clinical description, genetic mapping, and molecular characterization of Salla disease in an Old Order Mennonite population. *Am J Med Genet A.* 2005;138A(3):262–267.

31. Strauss KA, Puffenberger EG, Bunin N, et al. Clinical application of DNA microarrays: molecular diagnosis and HLA matching of an Amish child with severe combined immune deficiency. *Clin Immunol.* 2008;128(1):31–38.

32. Valasek MA, Repa JJ. The power of real-time PCR. *Adv Physiol Educ.* 2005;29(3):151–159.

33. Strauss KA, Morton DH, Puffenberger EG, et al. Prevention of brain disease from severe 5,10-methylenetetrahydrofolate reductase deficiency. *Mol Genet Metab.* 2007;91(2):165–175.

34. Dawkins R. *The Greatest Show on Earth.* New York, NY: Free Press; 2009.

35. Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: Genetic and metabolic testing on children with global developmental delay: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2011;77(17):1629–1635.

36. Farmer P. Rethinking health and human rights: time for a paradigm shift. In: Saussy H, ed. *Partner to the Poor: A Paul Farmer Reader.* Berkeley: University of California Press; 2010:435–470.

37. Kim JY, Farmer P. Global issues in medicine. In: Fauci AS, Kasper DL, Longo DL, et al, eds. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill; 2008:6–15.

38. Hawkins AK, Hayden MR. A grand challenge: providing benefits of clinical genetics to those in need. *Genet Med.* 2011;13(3):197–200.

39. Peabody FW. Landmark article March 19, 1927: The care of the patient. By Francis W. Peabody. *JAMA.* 1984;252(6):813–818.

40. Angrist M. Only connect: personal genomics and the future of American medicine. *Mol Diagn Ther.* 2010;14(2):67–72.

41. Samuels DC, Burn DJ, Chinnery PF. Detecting new neurodegenerative disease genes: does phenotype accuracy limit the horizon? *Trends Genet.* 2009;25(11):486–488.

42. Khoury MJ, Gwinn M, Ioannidis JP. The emergence of translational epidemiology: from scientific discovery to population health impact. *Am J Epidemiol.* 2010;172(5):517–524.

43. Farmer P, Léandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet.* 2001;358(9279):404–409.

44. Farmer P, Robin S, Ramilus SL, Kim JY. Tuberculosis, poverty, and "compliance": lessons from rural Haiti. *Semin Respir Infect.* 1991;6(4):254–260.

45. Harris J, Sulston J. Genetic equity. *Nat Rev Genet.* 2004;5(10):796–800.