The Science and Economics of Prevention

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CONSENT, OVERSIGHT, AND PERMISSIONS: All Clinic research is reviewed by the Institutional Review Board of Lancaster General Hospital and parents consent in writing to clinical research projects. Parents provided separate written consents to the publication of photographs in this manuscript. Figure 5 is reproduced with permission from Elsevier publishers.

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“If politics is the art of the possible, then science is surely the art of the soluble. Both are immensely practical-minded affairs. It is the professional duty of the scientist not merely to grapple with problems but to solve them.” P.B. Medawar, 1967.¹

“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, and that also means: to the actual size of man. Man is small, and therefore, small is beautiful” E.F. Schumacher, 1974.²

**ABSTRACT:** Despite major advances in genomic science over the last decade, its value in primary care remains controversial. The Clinic for Special Children was established in 1989 to provide care for uninsured Amish and Mennonite children with genetic disorders. It was built on the idea that population genetic knowledge could be integrated into local medical care to improve health outcomes and control costs. We examine the value—defined as health outcomes per dollar spent—of our genomics-based pediatric clinic with regard to four local determinants of medical spending: diagnostic testing, hospitalization rates, disability prevention, and palliative care. Clinic services reduce laboratory costs between 4- and 200-fold, shorten the time people wait for test results by 16,000 patient-days per year, reduce disease-specific hospitalization rates by 50 to 98%, and prevent major neurological disability in 11% of all Clinic patients. Each year the Clinic operating cost of 1.5 million dollars, which includes a 32 thousand dollar research budget used to map and develop testing for between 5 and 16 new pathogenic alleles, saves local communities 1.6 million dollars in laboratory fees, more than 8 million dollars in hospital costs, and 14 million dollars through the prevention of neurological disability. We show that integrating sophisticated genetic methods and subspecialty knowledge into regional primary care is effective and sustainable, in our case yielding a 15 to 1 return on investment. This approach is especially promising among developing nations and the many endogamous populations throughout the world.
GENES, MEDICINE, AND PEOPLE

Bridging the Gap

Genetic variation plays a role in virtually all human disease\(^3,4\) and most monogenic diseases begin during childhood.\(^5\) In a study of 5747 consecutive admissions to a pediatric hospital, 71% of children had illness that definitely or very likely had a genetic basis.\(^6\) In the developing world, children with genetic disease are often crippled or die without a correct diagnosis.\(^7\) This is tragic, because much genetically determined suffering is preventable and the tools for preemptive diagnosis exist.\(^8-10\)

Among the Old Order Anabaptist (Plain) people of the Eastern United States, knowledge of genetic risks has enabled better and more cost-effective health care.\(^11,12,9,13\) The non-profit Clinic for Special Children was established in 1989 to care for Amish and Mennonite children with genetic disorders.\(^14\) Early work focused on a few volatile conditions such as glutaric aciduria type 1 (GA1) and maple syrup urine disease (MSUD).\(^16,17\) In 1989, care for Plain children with these disorders was disorganized and costly; parents were uneducated about home management, traveled 100 miles during crises, and paid cash for services at rates 3- to 4-fold standard Medicaid reimbursement. Among Mennonites, childhood mortality from MSUD was 39% (N=36)\(^14\) and among the Amish, 94% (N=17) of children with GA1 were disabled by metabolic strokes mistaken for anoxic brain injury or encephalitis.\(^16\) These children were seldom if ever managed by the same physician twice and no improvements in care accrued from cumulative experience.

The Clinic was sited in a cornfield in Lancaster County, amid a large Anabaptist settlement, and built on a simple idea\(^9,13\): children with genetic disorders become unstable during the common illnesses encountered in everyday practice; subspecialty knowledge could be integrated into local medical care to define the services needed to prevent hospitalizations, catastrophic outcomes, and runaway costs (Fig. 1).\(^14,17\) It was an idea that stood in sharp contrast to the prevailing U.S. medical system, where general and subspecialty care were compartmentalized\(^13\) and both were separated in practice from the technological advances of molecular science.\(^18\)

Our 20-year clinical experience shows that bridging the gap between genetic methods, subspecialty knowledge, and primary care can be feasible and economically sound. This model works over the long term and becomes increasingly powerful as clinical and genetic insights accumulate in lockstep.\(^9\) To remain
vital, genetic research should address people’s most pressing needs.\textsuperscript{17,19} To be cost-effective, it should exploit the advantage of cumulative local knowledge.\textsuperscript{9}

\textit{Economics and Value}

The Clinic economy can be viewed against the background of U.S. health care spending (Table 1). In 2010, the Clinic spent 1.5 million dollars providing outpatient and laboratory services for 1877 patients (an average annual investment of $799 per patient) and offered testing for 103 different pathogenic alleles. The operating budget grows an average 3.6\% per year. One third is raised at annual quilt auctions organized by the Plain people. The largest of these, celebrating its 20\textsuperscript{th} anniversary in Leola, Pennsylvania, raised 310 thousand dollars in 9 hours through the sale of quilts, furniture, homemade food, and farm goods. One third of the budget represents philanthropic gifts and the additional third is fees. Ninety-five percent of our patients are uninsured (the Medicare Bill of 1965 exempts Anabaptists from contributing to or receiving benefits from social security)\textsuperscript{20} and the Clinic receives no state or federal money.

By comparison, 2010 medical spending for the U.S. population of 308 million people was 2.5 trillion dollars ($8,344 per person), half of which was paid by state and federal governments.\textsuperscript{21-23} This spending increases 6 to 7\% per year. The National Institutes of Health spent 31 billion dollars on biomedical research in 2010.\textsuperscript{24} Eight billion was categorized as research involving genetics; only 3\% of this was allotted to research on gene therapy or direct patient care.

How do we determine the \textit{value} of these expenditures? What benefit does the average U.S. citizen derive from $8,344 spent each year on her health care, and how well is this care distributed to those who need it most?\textsuperscript{25,26} How does 31 billion dollars of NIH research funding affect individual health and per capita medical costs? Does it ease the suffering of rural and uninsured people? Does it enable disease prevention?

Value, defined by Porter as “health outcomes achieved per dollar spent”, centers on what matters most to patients—survival, well-being, and independence.\textsuperscript{27} The denominator of cost encompasses a full range of medical services rather than narrowly focused specialty care. We will not attempt to measure the return on U.S. health care spending, but can examine the value of our rural health clinic over its 20-year history. Here, we apply Porter’s concept\textsuperscript{27} to local determinants of medical spending that can be quantified with some confidence: diagnostic testing, hospitalization rates, disability prevention, and palliative care.
MEASURING VALUE

Diagnosis

When parents of a disabled or ill child seek testing to determine the cause, evaluation at a tertiary center might include neuroimaging, electrodiagnostics, analytical and molecular tests, functional studies, tissue biopsies, enzymology, subspeciality consultations, and days or weeks of inpatient care. Each service is billed separately and it is not uncommon for tests to be repeated (e.g. sweat chloride, electroencephalogram, karyotype). These diagnostic excursions are often protracted and wasteful; each costs between 20 and 40 thousand dollars and has a diagnostic yield of 25-50%.28-30

Each year, the Clinic invests the equivalent of one such workup—about 32 thousand dollars--on microarrays and molecular probes that are used to map and develop testing for 5 to 16 new pathogenic alleles (Fig. 2). As a result, more than 100 genetic disorders can now be diagnosed in our office within 2 days for $50, precluding the need for a costly workup. For the restricted group of 23 conditions listed in Table 2, streamlined diagnosis saves local communities about 700 thousand dollars per year. Additional on-site testing saves families about 900 thousand dollars annually and reduces the time people wait for test results by more than 16,000 patient days per year (Table 3).14,27,31

Importantly, most of the conditions in Table 2 would never be diagnosed at a tertiary center because diagnosis is currently only possible by targeted sequencing of a population-specific allele (Fig. 2).9,13 Over a 20 year period this represents at least 10 million dollars of uninformative tests. For lethal disorders such as troponin myopathy (TNNT1, N=90), Amish microcephaly (SLC25A19, N=88), and sudden infant death and dysgenetic testes syndrome (TSPYLI, N=25), this diagnostic uncertainty prolongs a cycle of indiscriminate testing and invasive, futile management.

Hospitalization

Claude Bernard, writing in 1865, knew that “the first requirement . . . in practicing experimental medicine is to be an observing physician and to start from pure and simple observations of patients made as
completely as possible.”^32 In modern times, the control of genetic disease requires that presymptomatic diagnosis be followed by informed observation within a primary care framework.^13 Our practice is deliberately structured to allow for this. By studying children under a variety of conditions over long periods of time, we have learned to alter the natural history of many genetic conditions.^13

This can lead to profound savings. Consider just one disorder: classical MSUD. Before 1989, Mennonites born with MSUD arrived critically ill to regional pediatric centers where they stayed an average of 12 weeks. These hospitalizations cost 50 thousand dollars or more.^14 Beyond infancy each patient was hospitalized about once yearly for 7 days^33, which today would cost an average of $8,000 per day (range $1,000 to $38,000 per day).^34

Between 1989 and present, we have managed 68 Mennonite MSUD 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. Since 1989, progressive improvements in outpatient monitoring and treatment have decreased hospitalizations from 7.0 to 0.1 days per patient per year.^17,35 This 98.5% decrease in hospital costs applied to 81 MSUD patients under our care saves the community at least 4.3 million dollars annually—nearly three times the Clinic’s operating budget (Fig. 3).

**Disability**

Half of the disorders we manage damage the nervous system and many of these are treatable. Since 1989, we have been able to prevent neurological disability in at least 200 children, about 11% of the patients under our care (Figs. 1 and 3). In 2004, the Centers for Disease Control and Prevention estimated costs associated with four major types of disability: mental retardation, cerebral palsy, hearing loss, and visual impairment.^36 These estimates represent costs attributable to medical care, assistive devices, transportation, special education, and lost productivity of disabled individuals and their caregivers.

Table 4 shows CDC estimates extrapolated to 2010 dollars assuming an average national medical inflation rate of 6.1%.^23 Applied to 18 conditions for which dichotomous outcomes can be sharply defined, two decades of prevention have saved the Old Order communities about 270 million dollars. The Clinic’s
cumulative operating cost over this same period was 18.3 million dollars. The value of preventive care is much larger when applied to the full spectrum of regional medical problems.

**Looking Ahead**

Figure 4 shows projected savings from reducing testing, hospitalization, and disability over the next 10 years. These calculations assume that Anabaptist populations grow 5.5% per year and medical inflation continues at its current rate. Present investment in the Clinic pays off 15 to 1: operational spending of 1.5 million dollars saves the community about 24 million dollars per year ($12,800 per patient per year). Growing at an average annual rate of 3.6%, a 2020 Clinic operating budget of 2.1 million dollars could save the community as much as 83 million dollars, a 40 to 1 return on investment.

Money saved cannot be counted with certainty, but even if these estimates are off by an order of magnitude, the conclusion is the same: genomic science can now deliver great improvements in human well-being at acceptable cost, and can do so in the primary care setting. Whatever the exact balance of outcome and spending, the accounting exercise shows how a technological machine like U.S. healthcare can grow in cost and complexity without much accounting for its value, and also reveals how parts of that machine can be scaled down and adapted to provide better health care for less cost. Overall cost reduction depends, as Porter notes, on spending more on some services (e.g. diagnostics) to reduce the need for others (chronic care).

**A PLEA FOR SMALLER GENOMIC MEDICINE**

**Science to Scale**

The broad public health impact of the Human Genome Project has been slow to materialize. Although much attention is devoted to genetic mechanisms of disease, comparatively little is devoted to translating these insights into better care for individuals. Large scale genome-wide association studies are expensive, fraught with methodological problems and hard to interpret. They produce little actionable data and at great cost.

Much time and money are spent searching for gene variants that confer meager risks for common illnesses. Aggregating these risks may not improve predictive power when environment and behav-
ior (e.g. poverty, diet, exercise, alcohol, etc.) have such powerful effects. Whatever the potential value of large scale genetic research, it is also important to recognize that most of it takes place within corporate and university laboratories disconnected from local health conditions, clinical time pressure, and the day-to-day needs of patients. Such work often focuses on cultured cells and engineered animals because, compared to patients, they are more convenient and easier to control.

Translating genetic science into medical practice is messy and entails risk. Nevertheless, when individuals and families seek help for urgent medical problems, their needs should drive our research and shape how we use technology. Although some clinical laboratories offer DNA sequencing, few are poised to quickly map a new disorder or respond flexibly to the problems that face an individual patient. Fewer still translate this information into timely, affordable molecular testing. Because our lab was deliberately designed to work on this scale, we can provide families with meaningful clinical information at 10-40% the prevailing cost and in a fraction of the time (Table 3).

**Small Science and Public Health**

An abiding principle of the Clinic is to keep molecular research firmly rooted in the everyday practice of medicine. Thus as clinical services grow, the scientific mission remains focused on access, affordability, presymptomatic diagnosis, and prevention. In practical terms, this means that dangerous genetic conditions can be diagnosed on site within a few hours or days of life and treated locally to prevent hospitalization, untimely death, and brain injury (Fig. 1).

In Lancaster County, this has a measurable impact on public health: 41% of the disorders we manage can be treated decisively to prevent serious disease or disability and for an additional 36%, informed medical care allows children to suffer less and live more independently (Table 4, Figs. 1 and 3). The model is immediately applicable to the 1.7 to 2.5 million Anabaptists living in North America and other genetically isolated populations throughout the world. Extrapolated to a world of 6.7 billion people, one can estimate that at least 200 million individuals are afflicted with monogenic disease, 154 million can be treated to reduce suffering, and for more than half of these individuals--82 million people--presymptomatic treatment could have a decisive effect on their life course. But the world consists of many discrete subpopulations, each with its own genetic structure. The successful control of genetic
disease depends on exploring this diversity, defining risk within communities, and overcoming local ob-

   stacles to diagnosis and care.\textsuperscript{1,7,30,47}

   Critics will raise several objections: 1) For cost-benefit analyses, the Anabaptist demes are not comparable to the larger U.S. or world populations; 2) It is relatively easy to apply molecular methods within endogamous founder populations; one encounters more genetic complexity and thus clinical un-

   certainty in the outbred population; and 3) Monogenic (‘Mendelian’) conditions greatly simplify the application of genetic methods to clinical care. ‘Complex’ or multigenic traits—the common scourges of humanity— are a much harder problem for bioinformatics.

   These are valid objections, but this is just the point. On such a large scale, the task of linking hu-

   man genetic variation to disease is extraordinarily complex and, in some cases, insoluble.\textsuperscript{1} For genomic medicine to gain a foothold in the clinic, it must be broken into tractable parts by scaling appropriate methods to carefully selected individuals,\textsuperscript{63-65} families,\textsuperscript{66-68} and communities.\textsuperscript{69} Results will accrue that clarify what can and should be done to compensate for human genetic variation.\textsuperscript{9,70-77} This approach is especially promising in the developing world,\textsuperscript{62,78-81} Arab and Israeli nations,\textsuperscript{82} Nordic countries,\textsuperscript{83} India and other parts of Asia,\textsuperscript{84-86} and among Native American,\textsuperscript{87} First Nations,\textsuperscript{87,88} and other indigenous peo-

   ple.\textsuperscript{81,89}

   \textit{Complex Disease}

   Although some may view our research as trivial to the larger sweep of genomic medicine, it is in-

   structive to consider how it can inform fundamental problems in biology and guide “big” genomic science in clinically useful directions. The story of \textit{CNTNAP2} provides one example.\textsuperscript{73}

   In 2006, we discovered a homozygous 3709delG frameshift in exon 22 of \textit{CNTNAP2} among a group of closely related Amish children who suffered from complex partial epilepsy, autism and focal cortical dysplasia.\textsuperscript{29} Subsequent studies identified \textit{CNTNAP2} variants and intragenic deletions in non-

   Amish patients who had diverse clinical presentations, including idiopathic autism, epilepsy, language disorders, and schizophrenia.\textsuperscript{70-72,75} These discoveries kindled research into the function of \textit{CNTNAP2} during human brain development and revealed its role in frontal lobe connectivity and modulation of \textit{FOXP2}, a critical protein for the evolution of language.\textsuperscript{74,90,91}
We anticipate that the understanding of many other “complex” diseases (e.g. depression, obesity, type 2 diabetes, etc.) will also be enriched by focused regional studies. These 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 prove the key to revealing their basic genetic foundations.

The Care of Patients

There is another, less obvious reason why genomic science has not had a larger public health impact: 24 million dollars saved by one group of people is 24 million dollars profit lost to another. Human genomics research is now a reliable way for researchers to secure grants and for corporations to sell theoretical promise. Thus it can be primarily an engine of economic rather than medical progress. As new institutes of Personalized Genomic Medicine crop up in large corporate and university health systems across the nation and command massive intellectual and financial resources, it will be important to assess their value: the health outcomes achieved per dollar spent. It is safe to assume such centers will be cumbersome, inefficient and expensive. Saving patients time and money will probably not drive their operation and it is doubtful they will fundamentally change health care for most Americans.

Industry will continue to explore the promise of genomics in hopes of strong investment returns and universities will command expensive genetic technology to the extent that it is tied to institutional funding. These facts drive innovation and discovery in vital ways and can engender scientific and clinical excellence, but they also slow the spread of useful technology to the many underserved people of the world and the doctors who try to care for them. And although it would be unwise to allocate funding solely to practical field applications, as Guttmacher et al warned a decade ago: “stunning scientific and technological advances in genetics will mean little if they do not benefit people.”

Ultimately, genomics can only shape medical practice within a dense matrix of regional particulars and clinical facts. Vague or indeterminate clinical information often limits the utility of large association studies. 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 levels of biology—genetic structure, proximate environmental conditions, physiology, and culture—are inseparable for the purpose of understanding and treating disease.
them in practice can introduce blind alleys, wasteful spending, and unreliable data. This is most starkly expressed in the fact that among developed nations, the U.S. spends the most on genetic research but ranks last in quality of health care.\textsuperscript{107}

The Amish and Mennonite people are little educated about biology, science, and the politics of research, but everyday see and feel the effects of genetic disease in tragic terms. They naively ask: “Why would research doctors be interested in studying our disease but not be motivated, or able, to care for us?” Here, one must clearly distinguish the science of medical genomics, which appears to be flourishing, from the day-to-day practice of genomic medicine, which is not. A health care system that allows clinicians and molecular biologists to work side-by-side at an appropriate scale, concerned foremost with the care of patients\textsuperscript{108}, is the best way to insure that gene-based methods become a sustainable force in medical practice.\textsuperscript{105, 109} This will require a kind of teamwork that is not easily achieved in large-scale academic research or corporate health care, but has thrived in our small rural practice, where accountability shifted from productivity, grant funding, and “relative care units” to a candid assessment of how patients value services.\textsuperscript{110}
ACKNOWLEDGEMENTS

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REFERENCES

Clinic for Special Children

37. Kraybill DB. In; 2008.
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*Cost estimates are based on contemporary (2010-11) U.S. costs for standard imaging, laboratory tests, and related hospital services. Specific testing will vary with clinical presentation and regional resources. Estimates are: hypotonia/neuromuscular disease, $35,000; syndromic developmental delay, $27,000; and symptomatic epilepsy, $25,000.

†The number of new cases per year is based on current estimated birth incidence among populations served by the Clinic. Since 1998, we have identified an average of 8 new genetic conditions annually and an increasing proportion of these are novel.
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<tr>
<td>TUBGCP6 deficiency</td>
<td>$856,691</td>
<td>Blindness</td>
<td>4</td>
<td>$3,426,763</td>
<td>$171,338</td>
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<tr>
<td>Amnionless-B12 deficiency</td>
<td>$1,394,015</td>
<td>Quadriplegia</td>
<td>3</td>
<td>$4,182,044</td>
<td>$209,102</td>
</tr>
<tr>
<td>GJB2 deficiency</td>
<td>$631,166.21</td>
<td>Hearing loss</td>
<td>3</td>
<td>$1,893,499</td>
<td>$94,675</td>
</tr>
<tr>
<td>Weil-Marchesani syndrome</td>
<td>$856,691</td>
<td>Blindness</td>
<td>3</td>
<td>$2,570,072</td>
<td>$128,504</td>
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<tr>
<td>Classical galactosemia</td>
<td>$1,534,778</td>
<td>Mental retardation</td>
<td>2</td>
<td>$3,069,557</td>
<td>$153,478</td>
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<tr>
<td>Usher-like syndrome (HARS mutation)</td>
<td>$631,166.21</td>
<td>Hearing loss</td>
<td>2</td>
<td>$1,262,332</td>
<td>$63,117</td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>$1,394,015</td>
<td>Dystonia</td>
<td>2</td>
<td>$2,788,029</td>
<td>$139,401</td>
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<tr>
<td>EDNRB deficiency, hearing loss variant</td>
<td>$631,166.21</td>
<td>Hearing loss</td>
<td>1</td>
<td>$631,166</td>
<td>$31,558</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td>--</td>
<td>--</td>
<td>195</td>
<td><strong>$271,787,436</strong></td>
<td><strong>$13,589,372</strong></td>
</tr>
</tbody>
</table>

*Lifetime estimates for the cost of care are based on data from MMWR 2004;53:57-59, adjusted for medical inflation to 2010 U.S. dollars.

†This column lists the main preventable outcome associated with the diagnosis. For some conditions, multiple outcomes pertain (e.g., inadequate treatment of MSUD can result in spastic diplegia, cerebral palsy, and mental retardation). For other conditions (e.g., Usher-like syndrome), one outcome (hearing loss) might be treatable, whereas another (visual loss) may not.

¶For the purpose of these calculations, the main outcome of dystonia is considered comparable to cerebral palsy with regard to functional disability, dependence, and the need for medical services.
Table 4. Comparison of Price and Turnaround Time for Laboratory Services

<table>
<thead>
<tr>
<th>Service</th>
<th>Commercial Lab*</th>
<th>University Lab†</th>
<th>Clinic for Special Children Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid analysis</td>
<td>700</td>
<td>240</td>
<td>75</td>
</tr>
<tr>
<td>Organic acid analysis</td>
<td>247</td>
<td>230</td>
<td>85</td>
</tr>
<tr>
<td>Targeted detection of known mutation§</td>
<td>590</td>
<td>225</td>
<td>50</td>
</tr>
<tr>
<td>Complete gene sequencing, cost per exon¶</td>
<td>147</td>
<td>148</td>
<td>35</td>
</tr>
<tr>
<td>Cytogenetic microarray (DNA copy number)</td>
<td>1,654</td>
<td>1,550</td>
<td>600</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>$913,077.50</strong></td>
<td><strong>$1,314.13</strong></td>
<td></td>
</tr>
</tbody>
</table>

\*http://www.mayomedicallaboratories.com/test-catalog/

†http://www.bcm.edu/geneticlabs/

¶Costs represents averages from 9 genes ranging in size from 4 to 27 exons (range $73 to $253 per exon).

§For commercial and university labs, the cost of mutation detection varies; prices listed are averages. At the Clinic, the cost of detecting any mutation is the same, regardless of the method used (e.g. gene sequencing, real-time PCR, Light Scanner).

¥50 microarrays were performed for clinical copy number analysis, 95 were used for research (e.g. gene mapping).
Figure 1. Before 1989, Amish children with glutaryl-CoA dehydrogenase deficiency (GA1) were fully disabled by their second birthday and often misdiagnosed with cerebral palsy. The first genetic study at the Clinic for Special Children identified GA1 as the cause of “Amish cerebral palsy” in 16 children. Beginning in 1989, the Clinic offered on-site diagnostic screening, comprehensive pediatric follow-up care, and inpatient management. The incidence of brain injury decreased from to 36% by 1995. There have been no brain injuries among our 12 GA1 patients born after 2006.
Figure 2. The upper panel is an example of gene mapping, which consumes two thirds of a 32 thousand dollar annual research budget. Two Amish siblings from Pennsylvania were born with rib and spine abnormalities, cleft palate, and severe psychomotor delay. Their parents, rural farmers with no medical insurance, spent more than 20 thousand dollars at a regional children’s hospital on diagnostic testing for their daughter (left). By comparing DNA markers (SNPs) among the girl, her brother, and eight phenotypically similar children from Ohio, we mapped a novel disease gene (TMCO1) to chromosome 1 (arrow). The 10,000-marker mapping study was completed for a total cost of less than 2 thousand dollars; in contrast, evaluating each affected child at a tertiary medical center would cost about 270 thousand dollars in aggregate and yield no diagnosis. We developed a real-time PCR assay for the TMCO1 mutation and confirmed the brother’s (right) diagnosis in a few hours for $50. The lower panel shows the cumulative identification of pathogenic alleles in the Clinic’s core lab over the last 16 years. New technologies (e.g. microarrays, exome sequencing), once available, are quickly put into clinical practice.
Figure 3. The upper panel shows the value of reducing hospitalizations for just one disorder: maple syrup urine disease (MSUD). Before 1989, medical care for Mennonite children with MSUD was fragmented and expensive. Nearly half of affected children died of brain herniation and many who survived were permanently disabled. Early work at the Clinic led to affordable on-site amino acid testing, the development of home sick-day protocols, and on-demand MSUD parenteral solution for children who failed outpatient therapy. Preventative services for this one disease save the community about 3-times the Clinic’s operating budget each year. The lower panel shows the value of presymptomatic diagnosis. An Amish boy with severe psychomotor delay, spastic paraplegia, and arrested brain growth (left) remained without a diagnosis after extensive evaluation at a tertiary medical center. We subsequently identified a pathogenic change in the MTHFR gene (c.1129C>T), diagnosed three other disabled Amish children with this condition, and found a 30% carrier frequency within the Somerset Amish deme. In collaboration with the Pediatrix Screening Laboratory, we developed a real-time PCR method for detecting the MTHFR c.1129C>T allele in dried filter paper blood spots. Midwives began testing newborns for the mutation. The first child diagnosed by real-time PCR was sister to the proband (right). She started therapy her second week of life and has had normal brain growth and development during four years of follow up.
Figure 4. With medical costs growing at a rate of 6.1% per year, outpatient management strategies that reduce hospitalization and prevent disability have a powerful effect on community resources. A projected 2020 Clinic operating budget of 2.1 million dollars could save the community as much as 80 million dollars by eliminating unnecessary testing, reducing hospitalization, and preventing disability (blue).
Figure 5. An Amish girl born with alopecia, diffuse swelling, and thick inflamed skin nearly died of bacterial sepsis at 3 weeks of age, when laboratory studies revealed severe immune deficiency. We compared her homozygous DNA markers (lower panel, maroon peak) to overlaid homozygous peaks from seven healthy siblings (yellow peaks) and identified one 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 match HLA loci between the patient and her youngest sister. The entire process—from clinical presentation to genetic diagnosis to donor identification—took less than two weeks and saved the family between 40 and 80 thousand dollars. The child is alive and well four years after a stem cell transplant (Reprinted from Clinical application of DNA microarrays: molecular diagnosis and HLA matching of an Amish child with severe combined immune deficiency, Strauss et al., Clin Immunol. 2008 Jul;128(1):31-8, Copyright 2008, with permission from Elsevier).