Pediatric Otorhinolaryngology Today and Tomorrow

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All of Medicine is now in a process of substantial transformation. This contemporary matrix for Medicine in some ways can be seen as a revival of the essence of patient care. We have gone through a period of randomized controlled studies, meta-analysis, and the development of guidelines, all of which have looked at populations*.

Today our transformation rediscovers the individual. This transformation will result in what some call personalized Medicine and others precision Medicine † [1]. There are a number of the factors which are bringing this about.

The advances in biology which include genetics, work with stem cells and bioengineering have played a substantial role. Then there has been the astounding progress in technology which has brought about electromechanical implants, detailed imaging, some of which is tissue specific and enormous improvements in instrumentation. Another important factor has been a revolution in scale brought about by the capacity to handle information through the computer and the Internet. This includes the assembling of massive amounts of biological data, the tracking of patient data through electronic medical records, insurance records, public data, all of which have come through compiling information from individuals or by assessing large populations. The information revolution has also made access to knowledge universal, notably through the internet. Education has played a major role through simulation, which has become important both in training and in enabling "dress rehearsals" of complex cases. We now have our ability to monitor the skills and outcomes of individual physicians and practices so as to implement quality improvement. Society has played a role in the transformation by looking at the costs and benefits of what occurs in Medicine : outcomes are measured no longer just in terms of morbidity and mortality but by the complex metrics of quality of life.

Now let us examine how these transformations manifest themselves for pediatric otolaryngology. Let us begin in the area of communication disorders – hearing, voice, speech and language. Universal newborn infant screening became,

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† In the last two years there have been 28,041 articles indexed by pub med that have either mentioned personalized or precision Medicine

at least in the postindustrial world, the standard practice in the beginning of the 21st century[2]. This was enabled due to the discovery of cochlear emissions and the development of electronics which allowed for physiological assessment of hearing in newborns', otoacoustic emissions and auditory brain stem responses. These techniques, however, although they enabled tremendous progress in early diagnosis, could not identify those children who would have less than profound hearing loss, would first have hearing loss after birth, or those who would have increased susceptibility to extrinsic factors such as ototoxic medication.

Less than profound postpartum onset hearing loss has been documented in children with connexin mutations[3,4]. In 2010 the Brazilian group published[5] their data that demonstrated the utility of using a genetic screen at birth: a blood spot is routinely taken in all newborns for screening of various genetic disorders; in looking at all of those blood spots for genetic deafness genes, the Brazilian group found that they could identify infants who had the deafness genes, even though some of them passed the new born infant hearing screen. A very large scale study from China was published in 2011[6] which identified new born who carried a mutation which could result in hearing loss caused by an increased susceptibility to aminoglycosides[7,8]. They found that:

"To amaze us, the carrier rate for the mtDNA causative was 1.20% among newborns, high enough to call attentions in pediatrics ... genetic tests aid in the identification of newborn carriers of causative alleles, who tended to have a higher incidence of hearing loss and whose hearing health should be given more attention in clinic practice."

These two studies clearly demonstrate the utility of carrying out genetic screening on all newborns to determine potential deafness, regardless of whether they pass the newborn hearing screen, and if they are deaf to indicate the cause of deafness, and to identify those who may be susceptible to postpartum hearing loss. This should become the standard of care.

The identification of genetic mutations becomes even more important as gene therapy is being developed[9]. Once the diagnosis of deafness has been made, comprehensive genetic testing is essential and has become the new standard of care[10,11]. A recent study in the mouse[12] showed that a virus with an encoded genotype can be used to correct for the connexin mutation by preventing hair cell loss. Sooner rather than later, this form of therapy will be available for our patients and it will be essential that each newborn has a genetic screen in order to determine which will need to gene therapy and when.

Currently our care of infants and children with profound sensorineural hearing loss is the use of the cochlear implant. Recent studies have shown the physiological and the behavioral – real life – efficacy of bilateral implantation[13,14].These central nervous system observations are congruent with the improved musical abilities[15], sound localization[16], and every day listening performance of implanted children[17]. 75% of parents of the study population reported that their child had improved listening abilities. These and many other reports reinforce understanding of the benefits for quality of life and communication abilities in children who receive bilateral implants.

For many years[18] it has been well recognized that unilateral hearing loss creates a decrease in the ability to discriminate speech in noise. This often manifests itself in children by the presence of increased school difficulties as demonstrated by either being left back a year and/or the need for special services. A recent study[19] demonstrated that children with unilateral hearing loss have lower full-scale and performance IQ scores than children with normal hearing and also that there may be disparity in verbal IQ scores. These consistent findings of over three decades clearly mandate early intervention for these children. There are several forms of intervention, including the use of FM system, microphone and headphones in the classroom[20,21], cochlear implant into the affected ear[22,23], and bone conducting implants[24]. As we know now, through recent studies of critical periods in language acquisition and cognitive development, is essential that these children be identified and receive appropriate interventions as early as possible.

We now understand that language is a major concern to the pediatric otolaryngologist and a key outcome measure in assessing interventions. The measurement of expressive and receptive language is essential to be used in determining deficiencies, so as to enable appropriate interventions. It is a critical outcome measure for evaluating interventions as well[25-28]. We have quite effective tools for measuring both expressive and receptive language in children from birth through adolescence.[29-31], such as the Early Language Milestones Scale[32-34], etc. The evaluation of receptive and expressive language should be a fundamental part of the evaluation of all pediatric patients seen by the pediatric otorhinolaryngologist, so that appropriate and timely assessment of interventions for hearing, speech, voice, and/or language can be made.

To turn to another area, the care of the congenital hemangioma has undergone a substantial change with the publication from France of the preliminary results of propranolol therapy[35] in 2008. Within a year there were at least three reports of applying this dramatic therapy to pediatric otolaryngology[36-38]. The first case series, reported in 2010[39,40], showed that many but not all patients responded to the therapy. Some children became resistant and others relapsed so that surgical intervention was carried out. Most recently there was reported a large randomized controlled trial of propranolol and congenital hemangiomas[41]. The frequency of successful treatment was higher with this regimen than with placebo (60% vs. 4%, $P<0.001$). A total of 88% of patients who received the selected propranolol regimen showed improvement by week 5, versus 5% of patients who received placebo. A total of 10% of patients in whom treatment with propranolol was successful required systemic re-treatment during follow-up. Known adverse events associated with propranolol (hypoglycemia, hypotension, bradycardia, and bronchospasm) occurred infrequently, with no significant difference in frequency between the placebo group and the groups receiving propranolol. This report highlights that propranolol therapy will be effective in many, though not all patients. A retrospective European study had similar findings[42].

The possibility of a highly significant morbidity of neurological impairment has been noted[43-46] and pediatric otolaryngology has also become sensitized to the possibility of long-term sequelae with anesthesia[47,48] and radiation exposure[49,50] in

the infant. Whether this potential care associated morbidity will occur can only be determined by long-term follow-up. We have made a step forward in the care of the congenital hemangioma but still need to determine who will respond and who will not and the underlying mechanisms which cause these differences.

The most common and an extremely difficult pediatric otolaryngic tumor to care for is the juvenile angiofobroma. The treatment of these tumors has evolved over the last quarter of a century and now includes embolization[51] and various forms of surgical ablation. Currently, the use of radiation is, in the main, reserved for those tumors which are unresectable, because the long-term effects of radiation in a child are substantial and today's clinicians are aware of the sever sequelae and wish to avoid radiation where possible. During the last two years there have been at least three reports[52-54] concerning the molecular biology of these tumors which enables the clinician to predict which of these will be the most difficult to treat in terms of aggressiveness and recurrence, and should lead to modifications in intervention. A high expression of matrix metallopeptidase 9 (MMP-9), also known as 92 kDa type IV collagenase, 92 kDa gelatinase or gelatinase B (GELB) Higher MMP-9 was found to be associated with a poor prognosis for patients with juvenile angiofobroma who have been surgically treated54. These studies are leading to genetic intervention for the control and perhaps cure of the juvenile angiofobroma.

The restoration of an adequate airway in infants and children following congenital or acquired disease became a standard operative procedure through the initial studies and reports of doctors Fearon and Cotton[55-57] in the 1970s. Recently, a new approach has emerged: this is the development of various types of experimental scaffolds which may enable an extension of our ability to correct these lesions. One example of these studies is the rabbit model of Sin and colleagues from Korea[58,59]. They used allogenic chondrocytes cultured with porcine cartilage-derived substance (PCS) scaffold for partial tracheal defect reconstruction in rabbits. A powder made from crushed and decellularized porcine articular cartilage was formed as 5 mm x 12 mm (height x diameter) scaffold. Chondrocytes from rabbit articular cartilage were expanded and cultured with PCS scaffold. After 7 weeks' culture, the scaffolds were implanted on a 5 mm x 10 mm artificial tracheal defect in six rabbits. Two, four and eight weeks postoperatively, the sites were evaluated endoscopically, radiologically, histologically and functionally. None of the six rabbits showed any sign of respiratory distress. Endoscopic examination did not show any collapse or blockage of the reconstructed trachea and the defects were completely covered with regenerated respiratory epithelium. Computed tomography showed good luminal contour of trachea. Postoperative histologic data showed that the implanted chondrocyte successfully formed neo-cartilage with minimal inflammatory response and granulation tissue. Ciliary beat frequency of regenerated epithelium was similar to those of normal adjacent mucosa. They concluded that the shape and function of reconstructed trachea using allogenic chondrocytes cultured with PCS scaffold was restored successfully without any graft rejection. This and other similar studies[60-62] appear promising, and should lead to use in our patients. Unfortunately, a few of the human trials have been controversial in terms ethics and complete reportage of the patient's postoperative condition[63-65]. In one

instance[66], however, from another group, although the patient died 23 days after the implantation from an unrelated cardiac arrest, he was found to have an open, and stable tracheal transplant and intact anastomoses. Histopathological results of the transplanted tracheal graft during autopsy showed a squamous but not ciliated epithelium, neovascularization, bundles of alpha-sma-positive muscle cells, serous glands, and nerve fibers with S-100-positive nerve cells in the submucosa and intact chondrocytes in the cartilage.

Tonsillectomy is one of the most frequently performed pediatric otolaryngic operations. It may be carried out for variety of conditions including recurrent and tonsillar pharyngitis, airway obstruction as a contributor to obstructive sleep apnea, and other problems. The procedure is associated with significant postoperative morbidities including bleeding, dehydration, pain and the mortality rates have been reported from 0.002% in Sweden[67], 0.008% in Israel[68] to 0.020% in Australia[69].“Randomized control studies” have often been called the “gold standard” for evaluating medical treatments. Examining the literature, it was determined, in work of my own, that there were, by 2007, nine (9) tonsillectomy randomized control trials, with outcomes, measured in terms of infection, alleviation of airway obstruction, and/or quality of life[70]. The concept of a randomized control study speaks to the desirable goal of deriving objective data that will enable us to evaluate efficacy. Analysis determined, however, that although nominally “randomized”, not everybody was included. The range of patients finally included in these studies was the result of various modes of selection – this is not “random”.

The question arises: how did were these subjects chosen? These studies were analyzed to identify which risk factors for intrinsic and extrinsic susceptibilities to the disease and its sequelae were used to determine both inclusion and/or exclusion of subjects. The compositions of the studied populations, the cohorts, were analyzed to characterize the studies’ external validity. The risk factors included immune deficiencies, anemia, cardiac valvular disease, streptococcal carrier, peritonsilar abscess, craniofacial malformation, previous viral infections, learning and cognitive defects, obesity, failure to thrive, tobacco smoke exposure, access to medical care, and poverty. These risk factors were categorized as to whether they represented intrinsic susceptibility or extrinsic susceptibility, and whether they would result in either an intrinsic or extrinsic sequela. In 7 of the 9 reports, it was specifically stated that some of the risk factors were criteria for exclusion of subjects. All of the studies were performed in urban/suburban environments in post-industrialized nations. Of those studies that provided information concerning the social and economic status of their cohorts, their cohorts tended to represent patients from relatively well-educated families. Then, after these studies eliminated patients found unsuitable for various reasons, depending on the study, overall, only 60 percent of the individuals found suitable were went on to be enrolled in the studies, and, of these, 54 percent of those found suitable completed the study. According to available data, parental withdrawal or a change in intervention (e.g., an operation in a control subject or vice versa) occurred for 13 % of those who completed the studies. So much for “randomized.”

Among these studies, one became particularly influential, that of Paradise *et al*, in 1984[71] . This study proposed that eligibility for the tonsillectomy trials should depend on fulfilling four criteria which included that there had to be documented occurrences of tonsillar pharyngitis of seven or more episodes in the preceding year, five or more in each of the two preceding years, or three or more in each of the three preceding years. These conclusions were based upon the eligibility of 187 subjects, the total in the study cohort, out of a candidate population the researchers screened from 2,043 potential subjects. Talk about "narrowing down" – of these 187 "eligible" subjects, 97 rejected randomization and 91 accepted randomization. Thus the entire study – and its influential conclusions – are based upon 91 self-selected subjects. This is surely not a population from which the results can be applied to all children with the great variety of physical, medical, and socio-economic profiles. And, of course, the small number of subjects did not have the power to allow for identifying complications which occur over time and/or which are infrequent but potentially serious. Nor was the possibility of looking at what happened after the study period taken into account. The overarching problem of the criteria derived from this study is that intervention was recommended only after the child has undergone significant morbidity. The data from the Paradise *et al* report of 1984 was adopted either totally or for the most part for the creation and implementation of clinical guidelines for tonsillectomy and adenoidectomy in many nations including the United Sates[72], Europe[73], the Netherlands[74], United Kingdom[75], and Italy[76]. In retrospect it would have made more sense if resources had been focused on determining who would get sick before they got sick.

Studies demonstrate that when the guidelines have been applied, as in the United Kingdom, there has been a decrease in the number of tonsillectomies performed, which has led to an increase in morbidity associated with tonsillar pharyngitis[77,78]. Between 1991 and 2011, the overall tonsillectomy rate fell by 44%. In the same period, the admission rate for tonsillitis increased by 310% (Pearson's r=–0.67, p=0.01). The peritonsilar abscess admission rate rose by 31% (r=–0.79, $p<0.01$). Between 1996 and 2011, the overall tonsillectomy rate fell by 41% and the retro and parapharyngeal abscess admission rate increased by 39% (r=–0.55, $p=0.026$). There was a 14% overall increase in tonsillectomy and sore throat associated bed days. This was despite the large fall in tonsillectomy numbers and the reduction in length of hospital stay. The efforts to reduce the tonsillectomy rate were correlated with a significant rise in emergency admissions. The rise in the retro and parapharyngeal abscess rate is the most alarming due the very high mortality of these conditions. The bed day data for United Kingdom reveled that no net saving has been made.

These misguided criteria must be rejected. The clinician now must make the decision for tonsillectomy based on the totality of the patient – a personalized or precision determination. Fortunately, we have data that aids in making these decisions. The electronic medical record has been introduced in much of the postindustrial world, combined with a structured history, to help determine what symptoms or other conditions the child may have which would indicate that a tonsillectomy would be beneficial. The otolaryngologist needs to determine whether

or not the child has had recurrent infections, how often have they occurred and has the frequency of the infections increased or decreased. The many predisposing risk factors need to be taken into consideration, including genetic susceptibility to infection as evidenced either by direct genetic testing and/or association with phenotypic syndrome or characteristics. Information is needed as to whether the child has dysphagia and whether there is history of halitosis.

It is well-known that the quality of life is almost always improved after tonsillectomy. The problems concerning quality of life caused by tonsillitis need to be ascertained, such as how much school has been missed, how much work time has been missed by the caretakers, and how much pain and discomfort has the child undergone. The efficacy of tonsillectomy in the care of obstructive sleep apnea has been shown for many patients. The clinician must determine whether there are symptoms and signs of obstructive sleep apnea and to obtain objective data concerning the type of obstructive sleep apnea. Most obstructive sleep apnea is a combination of central and obstructive, and a sleep study can determine the contribution of each, giving the clinician information as to whether removal of tonsils and adenoids would be helpful. A history of a peritonsilar abscess or parapharyngeal abscess is critical in making the decision for operative intervention. The physical diagnosis must ascertain whether there is cervical lymphadenopathy, whether a tonsillar abscess is present, tonsiliths observed, and /or is there tonsil asymmetry. The inquiry must take into account the child's access to healthcare and, among co-factors, whether the child is living in an impoverished condition, which may indicate malnutrition. As knowledge of the genetic makeup of an individual and the epigenetic interactions is accumulated, we will be able to determine who will get severe infections before many of these occur. A twin study of 2005[79] and 2006[80] showed that that genetic effects explained 62% of the variation in the liability of recurrent tonsillitis, with the remaining variance attributed to environmental effects. There was no evidence of sex-specific genetic effects on the liability of recurrent tonsillitis.

The Italian report in 2007 by Grasso, Guerci, Zocconi, Milanese, Segat, and Crovella was the first to associate the mannose binding lectin - MBL2 00 genotype to recurrent tonsillitis when compared with the healthy controls[81]. These results were confirmed in 2009[82]. The Toll-like receptor gene (TLR) polymorphisms carriers of the TLR4 polymorphisms displayed an approximately 3-fold increased risk for group A beta-hemolytic streptococcus (GSA) and this association was more profound in patients with recurrent tonsillitis[83]. However, the presence of the TLR4-T399I polymorphism was associated with a 2-fold decreased risk of *Haemophilus influenzae* carriage. These findings indicated that in tonsillar infections, TLR4 polymorphisms predispose individuals to GAS infection, while they are protective against *Haemophilus influenzae* infection. The manganese-superoxide dismutase and glutathione peroxidase 1 polymorphisms (MnSOD Ala-9Val) was found to be significantly different for the controls versus the recurrent tonsillitis patients (P=0.009)., whereas no significant difference was found between the patients with tonsillar hypertrophy and the control group (P=0.369)[84]. In a study from Turkey, it was found that the MnSOD Ala-9Val polymorphism causes susceptibili-

ty to recurrent tonsillitis. This study suggests that there may be a possible relation between local and recurrent infections or inflammation of the tonsillar tissue and the MnSOD Ala-9Val single nucleotide polymorphism in pediatric patients with recurrent tonsillitis. There are now at least three genetic markers; mannose binding lectin - MBL2 00, Toll-like receptor gene -TLR4-T399I, and manganese-superoxide dismutase and glutathione peroxidase 1 polymorphisms MnSOD Ala-9Val - which can be used to predict which child may be affected. Hopefully these, with the further availability of inexpensive genetic screening, will be available to the otolaryngologist in making decisions on appropriate interventions. We have progressed from broad "herd" guidelines and randomized studies of the 20th Century to personalized, precision Medicine of the 21st Century.

Now to focus on the development that has given our specialty a particularly central role, both for individual health and the health of our society. It has to do with the fact that today, the ability to communicate effectively is of key importance for flourishing, for doing well. In our capacity for caring for and optimizing hearing, voice, speech and language, the burden for enhancing success, individually and as a society, lies on us with particular pertinence. Put another way, technological and social change has brought about a redefinition of those famous words, "The survival of the fittest." Today, "fittest" applies not to, say, great physical strength or even manual dexterity: Steven Hawkins, to take a notable example, is deficient in both and yet, in Darwin's terms, he has produced healthy offspring. Perhaps an even more stunning example is Richard Glatzer, the film director suffering from late stages of ALS who has died recently: he was able to move only one finger when directed "Still Alice," which won the Academy Award for his lead actress. Fitness now applies to the ability to communicate effectively, well, and optimally. And that is what we Pediatric Otolaryngologists enable.

Consider that back in 1900, 80% of the population was employed as farmers or they held blue collar jobs. They made their living by the sweat of their brows – like Adam -- and by their hands -- manual labor. The other 20% of the population had white collar jobs: their livelihoods were gained through their communication abilities. At that time, public health initiatives were focused on nutrition and infectious diseases – you required a strong and healthy population to bake the bread, sew the hem, mine the coal, harvest the wheat and carry the bricks. But the only constancy in life is change and employment patterns are no exception. By 1950 the manual labor force decreased to 60 % with then 40% of employees' dependent on their communication skills. And, as we entered the new millennium, rightfully called "The Communication Age," white collar employment accounted for 75% of the labor force, and of the remaining 3% were farmers and 22% blue collar workers. Drilling down on these numbers reveals that many of the so-called manual labor group, farmers and blue collar, are now utilizing communication skills to maintain their livelihoods. Farming today in developed nations has much less to do with physical labor, and requires much more complex planning, resource allocations, and fulfilling the myriad of rules and regulations. The iPad - smart phone - has replaced the pitch fork. As for blue collar labor, much if of it today is concerned with monitoring robots and automated assembly lines. In 1900 it took

303 person hours to build an automobile: today it takes 20! Charlie Chaplin's Modern Times is but an excellent nostalgia. I would imagine that today's Modern Times, instead of showing a frenetic assembly line worker, would show a worker hysterical over lost passwords! Prediction of the growth of new jobs in the communication age indicates a 92% increase for communication based jobs such as administrative assistants, elementary school teachers, registered nurses, retail salespersons, bookkeepers, accountants, and auditors, etc. Very few new jobs are projected for manual laborers since, after all, a machine digger now operates with 37 laborers and does the work formerly requiring 7,000 pick and shovel men; an ensilage harvesting machine cuts cornstalks in the field and feeds them to the silo without a single human being handling the stalks. Given the great need for workers with good communication skills, it is essential to consider the incidence and prevalence of these disorders.

In the United Sates the prevalence of hearing loss is 8.6%, for voice and speech disorders 9.5% for language disorders; in children it is conservatively 7.4%. Overall about 9% of the population suffers from a communication disorder and the percentage affected increases with age. What is the effect of these communication disorders on individual? Only 58% of those suffering from communication disorders are employed, compared with 75% of the total population employed. Those unable to speak clearly have twice the unemployment rate of the rest of the population. Adding insult to injury, those with communication disorders are three times as likely to be at the lower end of the income scale; they have a median income of about half that of the rest of the population. So, communication disorders result in more than 9% of the population having twice the unemployment rate of the rest, and with half the median income – a disturbing picture for, what are today, many treatable conditions, and a great drain on society. The health of nations – thank you Adam Smith - is now, in the 21st century, dependent upon the maximization of communication: the hearing, voice, speech, and linguistic - capacities of the work force. We, as otolaryngologists, know that these abilities are biological phenomena. The focus of the nation's public health must and will be directed to the prevention, cure and care of these communication diseases, most of which have their origins in the child, with their deleterious sequelae in the adult. We, the pediatric otolaryngologists, are the doctors responsible to implement this.

In addition to changes brought about by technology, the aging of the population is highly pertinent[85]. In 2050 we will by all projections have many fewer workers for each dependent person – young and old -- than we do today. As the U. S. bureau of labor statistics states, there will be "dramatic downward shift in the availability of potential workers relative to people outside the normal working age." China, in response to these projections, has just recently changed from its "one child" allowed for a couple to "two," to avoid running out of workers in the future. In 2050 there will be about 10% to 15% fewer workers to support the entire population. The number of worker retirees – the potential support ratio (PSR), which is equal to the number of people aged 20 to 64 divided by the number of people 65 and over for the United States is at present is 4.6: this is projected to

decline to 3.5 by 2050 and to 1.9 by 2100[86]. A similar situation has been calculated for Europe[87] where it is calculated that between now and 2050, the number of those of working age per older person 65+ will halve from 4 to 2."

As we live longer and have fewer children, the percentage of working-age individuals will shrink. The United Nations projects that by 2030 the number of workers globally to per older person will decrease from 7 to 4.9[88]. 2016 data from the United Nations predicts that for the more developed nations, in 2050 there will be 7.3% fewer workers from age 15 to 64 to support an 8.8% increase in people 65 years of age or older. Thus each worker must produce an increase of 16.1% economic wealth just to maintain the status quo of 2016. Since the prevalence of communication disorders results in unemployment of about 4.5%, then if these conditions are not ameliorated the workforce of 2050 will have to produce 20% more economic wealth to maintain the status quo – and we're talking about calculations made for a mere twenty-five years from now.

This projection of more elderly supported by fewer workers, dictates the primary importance of prevention and cure of communication disorders which, in the main, originate in the earliest phases of life: in the economic sense, each new born now becomes more precious and society will demand that each new child be enabled toward optimal communication abilities so as to become an economically productive person.

Redefining survival of the fittest pertains not only to individuals but to societies. Compassion for the individual and societal benefit here follow the same path. The fittest nations will be those that optimize their populations' communication abilities. If individuals of our population and a nation are to be the fittest so as to survive in the communication age, the prevention, cure and care of communication disorders must be a primary public health mission in the 21st century. This is the calling of the pediatric otolaryngologist. The pediatric otolaryngologists are the physicians uniquely positioned to ameliorate and cure many of these disorders by early diagnosis and treatment of the child.

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