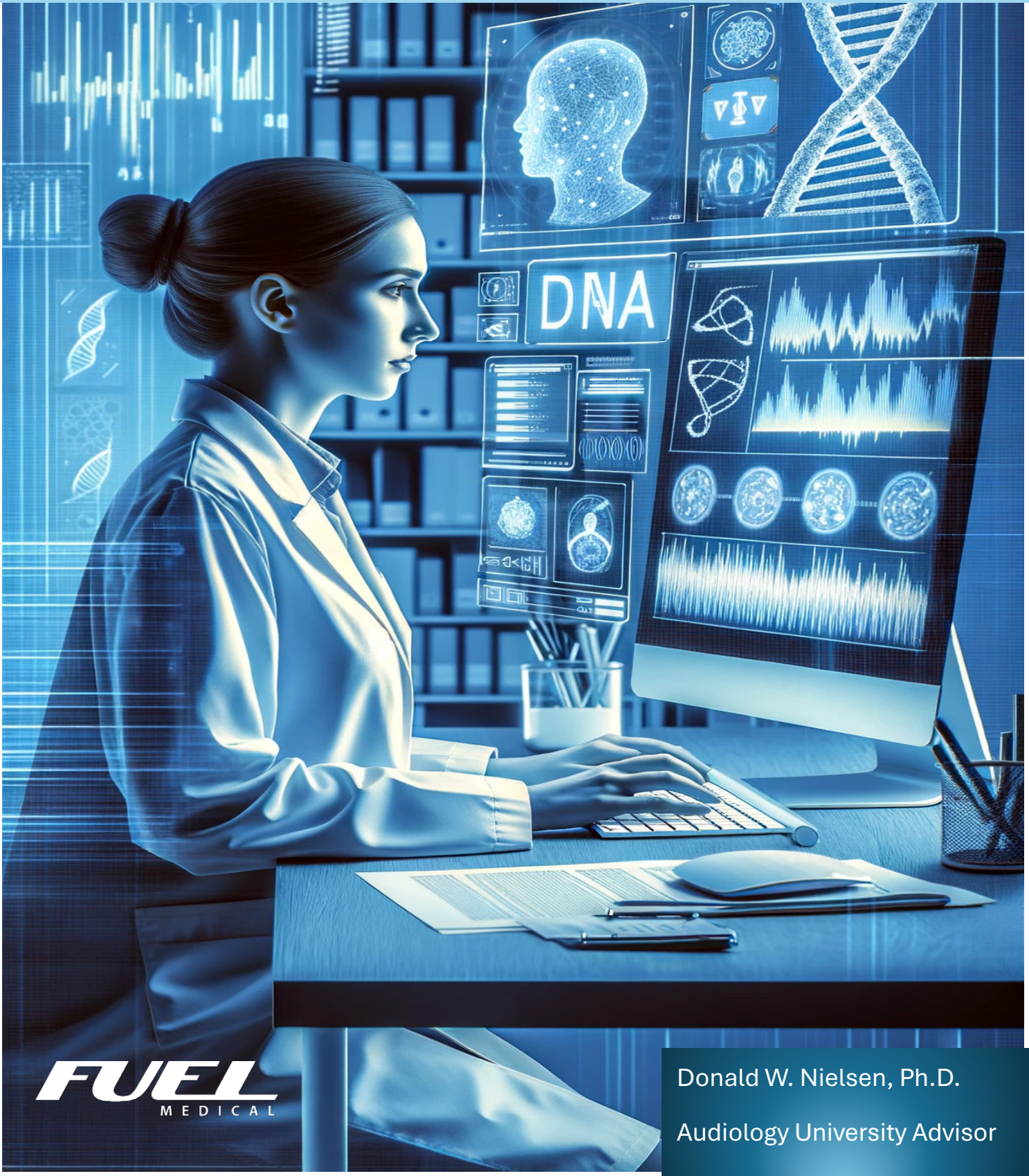
FUEL YOUR FUTURE

Genomics and Precision Medicine: The Astonishing Revolution of Hearing Health Care

A Call to Action for Audiologists!



FUEL MEDICAL

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Genomics and Precision Medicine:
The Astonishing Reinvention of Hearing Health Care

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A Fuel Medical Group
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INTRODUCTION

"The power to become habituated to his surroundings is a marked characteristic of mankind." —John Maynard Keynes

The expectation that tomorrow will be like today is a profound human bias. It is a powerful heuristic tool because it has been almost always correct. Almost! For example, the expectation of little change was radically disrupted at the birth of the 20th century.

New ideas and technologies during the late 19th and early 20th centuries completely revolutionized the U.S. economy. This triggered the development of mechanization, mass production, the arrival of electricity, lighting and telephones, and other significant advancements. The current era is defined by the rapid development of cutting-edge technologies that prioritize intelligence and personalization, leading to a transformative impact on the economy, with health care being a prime example. The most challenging aspect to grasp and admire is the rapid pace at which these technological changes are improving. Rapid changes are taking place.

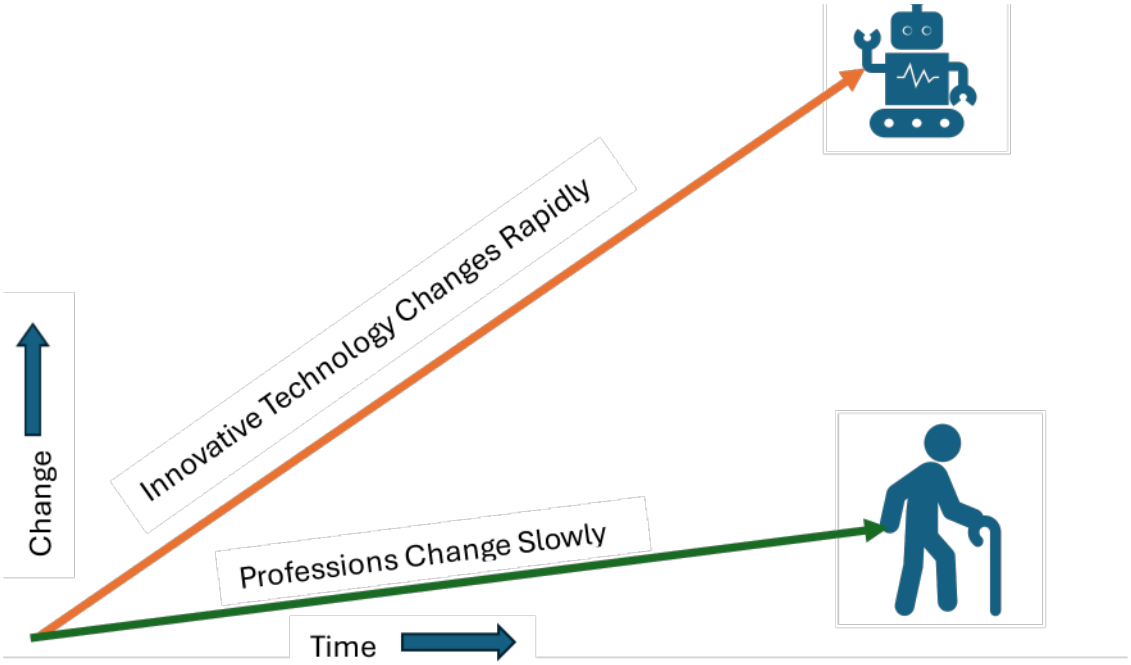


Figure 1. Innovative technologies change rapidly, but professions change slowly.

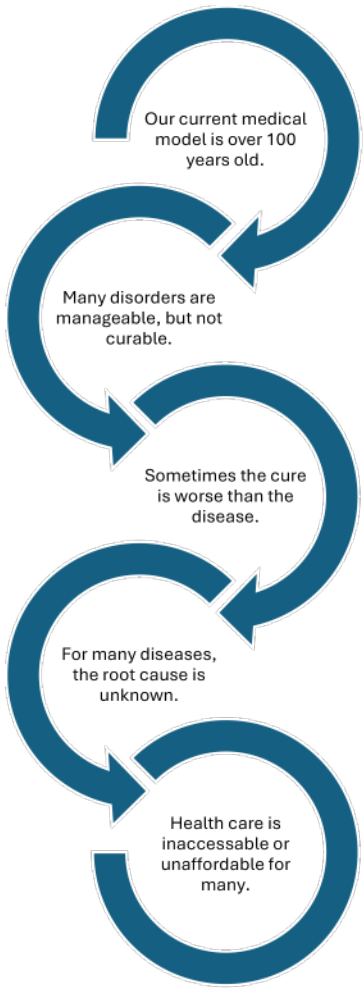
While innovative technology changes rapidly, professions, stifled by tradition and self-interest, change slowly (Susskind, D., 2020; Susskind, R., Susskind, D., 2022). As time passes, the gap grows between flourishing technologically driven advances, like artificial intelligence (AI) and genomics, and audiology's ability to keep pace. We have the opportunity and responsibility to close that gap.

Closing the gap is not easy. These transformations are disruptive, even destructive, of best practices and current health care and business models. They involve radical change and introduce promising alternatives to traditional practice. Fasten your seatbelts!

Get ready to discover the astonishing reinvention of hearing health care. As an audiologist, you have the power to become a true changemaker in this field. This comprehensive guide will take you through the latest developments and techniques. You won't believe what you can achieve when you embrace the power of innovation and cutting-edge technology—prepare to transform your profession and the health care of your patients!

HEALTH CARE PROBLEMS INNOVATIVE TECHNOLOGIES MUST SOLVE

Our health care system is the most expensive in the world. Its global ranking is 28th, and among developed nations, it stands in last place, primarily because of the high costs and limited accessibility resulting from the absence of universal health care coverage. Let's take a closer look at some of its most challenging weaknesses we can now eliminate.



One-size-fits-all medicine does not work well!

Traditional medical approaches based on broad population averages often miss the mark because they do not account for the individual differences that are critical for effective and safe medical care.

We need a personalized approach to identify who will benefit from clinician-recommended treatments and who will not, sparing them from unnecessary expense and side effects.

Figure 2. Reasons our current medical system fails many people.

In addition to the explanations in Figure 2, we are aware that the aging population is creating a growing need for health care. This is a challenge because there are not enough medical professionals. This scarcity limits people's access to medical guidance and treatment. It's not just about access but also about where people can acquire medical knowledge. The traditional method assumes that only professionals have specialized knowledge, which prevents critical information from reaching those who can't reach out to professionals.

Relying solely on professionals can also discourage patients from investigating their health issues and engaging in their health care, leading to feelings of self-doubt about their independence. However, we now have the technology to supplement professionals, engage patients and spread health care expertise at a lower cost (Nielsen, 2024). As medical professionals, we have a duty to make this happen.

Embedded in our flawed national health care system resides hearing health care, which also has problems driving the need for its reinvention.

HEARING HEALTH CARE PROBLEMS INNOVATIVE TECHNOLOGIES MUST SOLVE

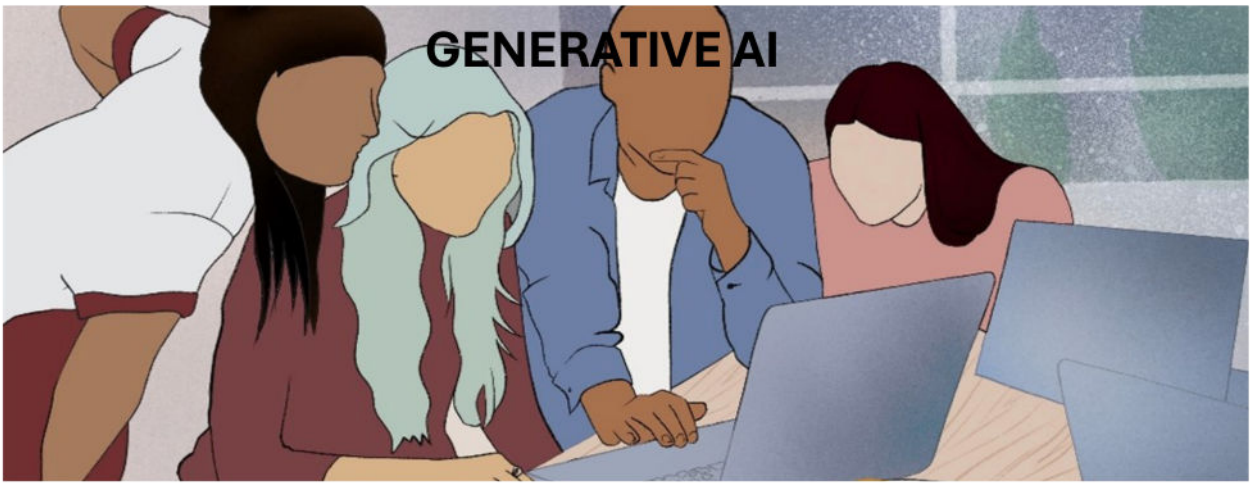
Here are the chronic problems of hearing health care:

- There is a supply and demand inequality consisting of vast patient demand and limited provider supply.
  - According to the NIDCD, about 37.5 million people report having some trouble hearing. If we add in those who self-report hearing issues but have normal audiograms, the number could be 60 million.
  - To serve them, we graduate about 800 Au.D.s annually and have a constant workforce of about 12,000.
  - We also have a constant workforce of about 12,000 ENTs, of which 5,948 are general ENTs and 1,324 are neurotologists. The remaining 4,728 deal with pediatrics and non-otologic specialties.
- Among those aged 70 and older with hearing loss who could benefit from hearing aids, only 30% have ever used them.
- For adults aged 20 to 69 who would benefit from wearing hearing aids, only 16% have ever used them.
- Traditional interventions such as hearing aids and implants do not fully restore normal hearing.
- Access, affordability and acceptability of traditional treatments are not satisfactory.
- Comorbidities and disease interdependence are now being acknowledged as important to hearing health care. We must incorporate this information into our patient care.

Numerous problems exist within the health care system, including those related to hearing health care. These issues are the driving force shaping the reinvention of health care, which incorporates three new technologies that are blossoming simultaneously and will solve these problems (Metzl, J., 2024).

NEW TECHNOLOGIES DRIVING HEALTH CARE'S REINVENTION

Let's examine generative AI, big data analysis and genomics, which are the three main contributors to health care's reinvention.



Generative AI (genAI) is a form of machine learning based on deep learning and has more capabilities than basic AI. It can generate new content responding to a prompt by identifying patterns in massive quantities of training data and then creating original material with similar characteristics. Outputs from genAI models can be indistinguishable from human-generated content. GenAI can be used out of the box or fine-tuned to perform specific tasks.

The transformational potential of genAI for hearing health care lies in its ability to:

- Enhance diagnostic accuracy and disease tracking.
- Improve the prediction of patients' outcomes.
- Suggest better treatments.
- Streamline hearing clinic processes.
- Catalyze innovation.
- Enhance patient engagement and experience.
- Enhance the accessibility of hearing health care delivery by remotely triaging patients.
- Reduce hearing health care costs.
- Improve patient outcomes.
- Facilitate personalized learning experiences for patients and students, making education more accessible and engaging.

While these attributes facilitate hearing health care provision, genAI is also breathing life into precision medicine, making it practical for personalized patient care. We will discuss this in more detail shortly. I strongly recommend reading "The Intelligence Revolution In Hearing Health Care Delivery" (Nielsen, D.W., 2024) for more specific information on genAI and its influence on health care delivery and virtual providers.

Big data refers to massive datasets that are too large and complex for human cognition or conventional data-processing software to manage effectively. The three defining characteristics of these datasets are volume, velocity and variety (Sherry T., 2024).

Volume pertains to the vast amounts of data produced from diverse sources, such as electronic medical records (EMRs), research data, sensors, mobile devices, wearables, home-based therapeutics, etc. The magnitude of data collection is evident in the units used to measure it, such as terabytes, petabytes and even zettabytes.

Velocity refers to the rate at which this data is generated and processed. With the advent of the modern digital age, data is pouring in at an unprecedented rate from sources like patients' medical portals, Internet of Things (IoT) devices, medical journals and online transactions, which calls for real-time processing and analysis.

Variety is data that can be found in a wide range of formats, such as structured numeric data typically stored in databases, as well as unstructured text files, videos, emails and various other types. Due to the diversity of data, additional preprocessing is necessary to extract meaning and ensure data usability.

Advanced analytic techniques are utilized in big data analysis to effectively handle and extract valuable insights from large and diverse datasets. This process plays a critical role in discovering hidden patterns and correlations

in patient data, genomic data, research data and other medical sources.

There are several crucial steps involved in analyzing big data.
Data Collection: The process of gathering extensive volumes of information from diverse sources.
Data Storage: Efficiently storing the collected data using technologies like cloud-based services.
Data Processing: Employing advanced processing techniques to handle the complexity and speed of data.
Data Analysis: Applying analytics and machine learning algorithms to extract insights.
Visualization and Decision Making: Visualize the results and make informed decisions based on the analyzed data.

Big data analytics drives better decisions, enhances efficiency and creates personalized patient experiences. It plays a crucial supporting role in personalized medicine.

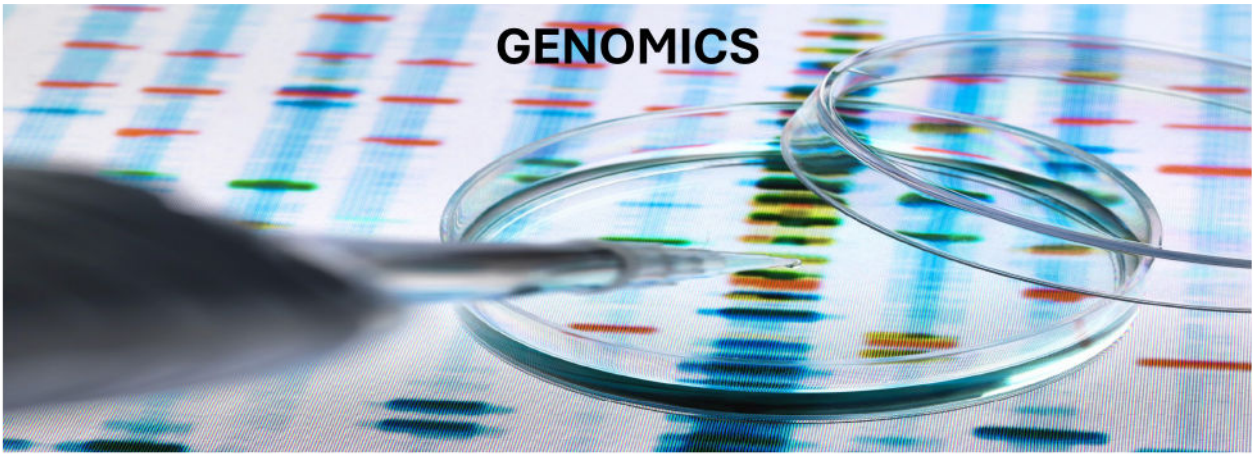
Real-world applications of big data in medicine are diverse and transformative, significantly enhancing the ability to diagnose, treat and manage diseases more effectively. Here are some key applications:

1. Predictive Modeling in Health Care
2. Enhanced Diagnostic Tools
3. Real-Time Health Monitoring
4. Improving Clinical Decision Support Systems
5. Management of Health Care Services
6. Genomic Data Analysis for Targeted Therapies
7. Drug Development and Personalized Medicine

These applications demonstrate the profound impact of big data on medicine, offering significant improvements in patient care, treatment personalization and health care management.

Next, we will consider genomics, the most potent tool in the reinventor's personalization tool kit.

Genomics involves examining an organism's entire DNA, including all its genes. The focus is on genomes' structure,



function, evolution, mapping and editing.

It includes examining genetic sequences and allows us to research how genes are structured, interact and impact patients. It entails analyzing all genes' overall attributes and measurable aspects, how they are connected and how they collectively influence the patient's growth and development.

The progress in genomics has been driven by the development of technologies that enable fast and cost-effective DNA sequencing and analysis, which is central to transforming medicine. The cost of sequencing the first human genome was about $3 billion, and it took several international institutes, hundreds of researchers and 13 years to complete (https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost). Today, it can be done for $100 (Albert, H., 2024), unlocking the full potential of the human genome. Genomics is poised to significantly improve health care across multiple dimensions, from enhancing diagnostic accuracy to personalizing

treatment strategies and preventing diseases. A patient's medical records should routinely include their sequenced genome.

The transformational potential of genomics for health care lies in its ability to:

1. *Predict Disease Risk:* This predictive capability enables preventive measures to be taken before the onset of symptoms, potentially preventing the development of diseases or significantly altering their course.
2. *Enhance Diagnostic Accuracy:* Genomics enables the precise identification of genetic mutations responsible for diseases. This can significantly reduce the time and resources spent on trial-and-error approaches to understanding a patient's condition, leading to faster and more accurate diagnoses. By identifying genetic predispositions to diseases, health care systems can implement targeted screening strategies that improve early detection and provide interventions at the most treatable stages.
3. *Personalize Treatment Plans:* Genomics facilitates the development of personalized treatment plans tailored to individual patients' genetic profiles.
4. *Enable Pharmacogenomics:* Genomics enables health care providers to prescribe drugs that are more effective for the individual based on their genetic makeup, minimizing adverse drug reactions and improving therapeutic outcomes.
5. *Reduce Health Care Costs:* By enabling more precise diagnostics, targeted treatments and effective prevention strategies, genomics can lead to a more efficient use of health care resources, potentially reducing overall health care costs. Early intervention and personalized treatment plans can decrease the need for extensive and expensive care later.

These three emerging innovative technologies—genAI, big data analysis and genomics—are interacting and maturing simultaneously to give life and consequence to precision medicine.

PRECISION MEDICINE

Precision medicine considers individual variability in genes, environment and lifestyle for each person and targets the right treatments to the right patients at the right time. It utilizes large datasets, including lifestyle, medical and genomic information, to make health care more personalized and effective. This approach allows doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It contrasts with a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals (Cerrato, P., & Halamka, J., 2018).

GenAI, powerful computers, the routine collection and sharing of e-medical records, big data analysis and genomics, have energized precision medicine and made it practical. Here is how:

Generative AI and Powerful Computers: Generative AI's (genAI) ability to absorb and rapidly analyze massive data sets too complex for human cognition has turbocharged precision medicine and genomics, and both benefit when their data sets increase.

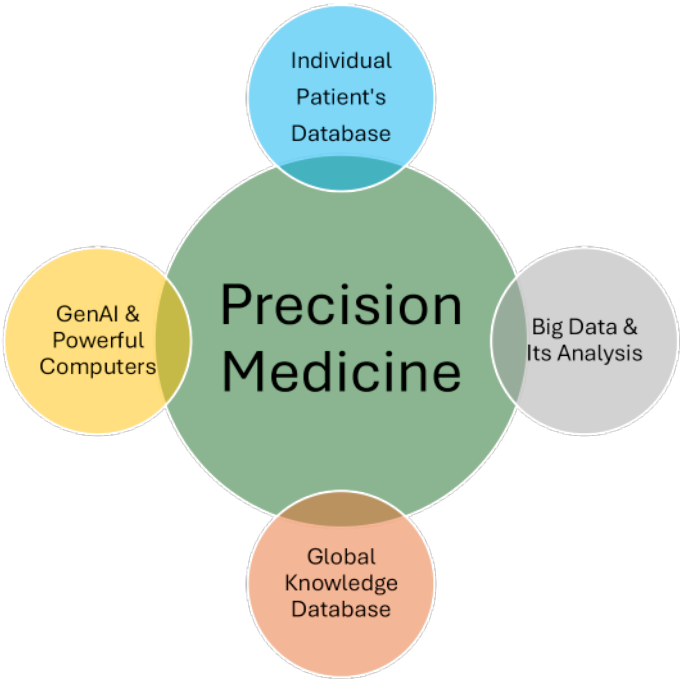


Figure 3. The building blocks of precision medicine.

Big Data & Its Analysis: The impact of massive data from diverse sources such as electronic medical records, wearables, genomics, lifestyle records and research on health care is immense. These data sets exceed humans' ability to analyze them. But with the aid of genAI and powerful computers, we can now enable big data analysis, allowing us to retrieve, analyze and apply the interrelated wisdom of these diverse data sets.

Comprehensive Individual Patient's Databases: Robust databases for individual patients provide a wealth of information, such as lifestyle, environmental factors, wearable medical device data and genomic sequence, that enables us to tailor diagnoses and treatments more effectively.

Global Knowledge Databases: The global knowledge databases are constantly updated with information on diseases, symptoms, cures and research from around the world. These databases are continuously upgraded to track the responses of patients with similar individual data to different treatments.

Advances in genomics are central to precision medicine and allow us to personalize disease prediction, prevention, cure and treatment. GenAI, powerful computers and big data systems have combined with genomics to enhance the quality of life and unleash the life-preserving magic of precision medicine.

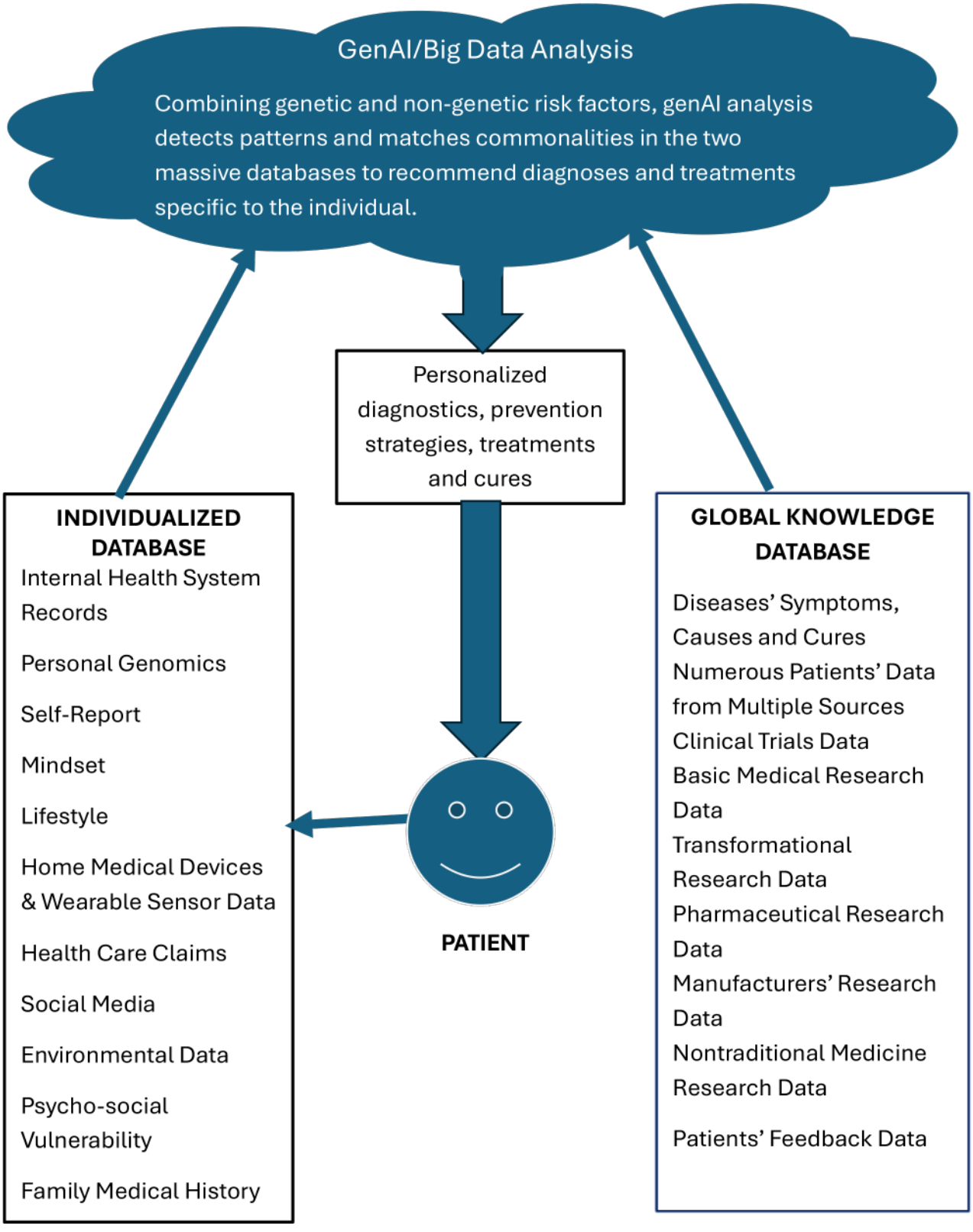
HOW DOES PRECISION MEDICINE WORK?

Precision medicine is a new term that encompasses emerging approaches to disease treatment and prevention based on individual variations in genetics, environment and experiences (Rudman et al., 2018).

Precision medicine is new to audiologists but not unfamiliar. Audiology has always focused on personalizing hearing treatments—we tailor the first fit of a hearing aid to the patient's audiogram, and real-ear adjustments customize treatment to the patient's ear canal. But precision medicine pushes customization to the extreme.

Precision medicine gathers extensive data, including information about an individual's health, lifestyle and environment, and a vast global knowledge base about disease mechanisms. It then analyzes this data, identifying patterns and using them to make predictions and recommendations. The goal is to provide personalized patient care.

THE PRECISION MEDICINE ECOSYSTEM



THE BENEFITS OF PRECISION MEDICINE

Precision medicine is revolutionizing health care by making it more predictive, preventative, personalized and participatory. Here is how:

Targeted Treatment: Precision medicine tailors medical treatment to individual characteristics, increasing the effectiveness of treatments.

Early Disease Detection and Prevention: Precision medicine enables early detection of diseases. By taking a proactive approach, we can prevent diseases from progressing, potentially saving lives and reducing health care expenses.

Customized Medication Dosages: Precision medicine allows for the customization of medication dosages to optimize efficacy and minimize adverse reactions, improving medication adherence and reducing the risk of complications.

Enhanced Patient Engagement: Precision medicine empowers patients by involving them in their health care-related decision-making processes. Access to personalized genetic information and treatment options makes patients more engaged and motivated to actively participate in their own care.

Improved Patient Outcomes: Precision medicine will improve patient outcomes by customizing treatments, which produce higher treatment success rates, reduce side effects and improve overall health outcomes.

Reduction in Health Care Costs: Although initial implementation costs may be higher, precision medicine has the potential to reduce long-term health care costs by avoiding ineffective treatments, minimizing hospitalizations and preventing disease progression through early intervention and prevention strategies.

Advancement in Research and Development: Precision medicine contributes to the advancement of medical research and development by providing insights into the underlying mechanisms of diseases and individual responses to treatments. It positions audiologists to effectively treat the heterogeneous causes and manifestations of hearing loss on a more effective individual basis.

Precision medicine clearly has tremendous benefits, but it also faces challenges.

The fundamental challenge is assimilating, analyzing and integrating genomic data, electronic medical records (EMRs), data obtained with mobile health devices and other data about hundreds of millions of people.

Another essential challenge is the shortage of AI-ready data, which slows the adoption of AI, machine learning and precision medicine. Preprocessing will be necessary to extract meaning and ensure data usability from many data sets.

A third essential challenge is ensuring appropriate participant inclusion regarding ethnic diversity and other demographics and the inclusion of the medically disenfranchised without EMRs or ready access to the Internet.

Finally, users of precision medicine must address privacy and security concerns.

WE MUST BRING THE POWER OF PRECISION MEDICINE TO HEARING HEALTH CARE.

Precision medicine represents a momentous shift toward more individualized care and the promise to revolutionize health care. Powerful computers armed with genAI and the massive data sets of precision medicine are revealing long-hidden relationships, enlightening us with new knowledge about the causes and effects of diseases and health care and how to perfect it.

The breadth of precision medicine is creating new partnerships between scientists in a wide range of specialties, as well as people from patient advocacy communities, universities, pharmaceutical companies and others.

Within precision medicine, genomics is the most powerful tool for personalizing hearing health care and preventing, treating or curing diseases; it is essential. However, under our traditional system, genomics data is rarely available for audiologists, and few treatments are available to slow or reverse genetic deafness in the clinic, despite the fact that genetic hearing loss accounts for 50% of congenital sensorineural hearing loss (Allen Young; Matthew Ng., 2023; Omichi, R. et al., 2019).

The remaining hearing loss is due to environmental or acquired causes, such as infection, trauma, noise exposure and ototoxicity, which may also have some genetic involvement. Diagnosing and treating hearing issues must include the possibility of genetic prevention, cures and treatments. Precision medicine enables us to do that (Sprinzl, G. M., 2022).

So, let's examine how genomics is revolutionizing hearing health care.

HOW GENOMICS IS REVOLUTIONIZING HEARING HEALTH CARE

GENE THERAPY

Gene therapy, a medical approach that utilizes genetic material to treat or prevent diseases by correcting the underlying genetic problems, involves modifying a person's genetic makeup, usually by introducing new genes and repairing or replacing faulty genes within the body's cells. Gene therapy can be administered in two primary ways: in vivo (directly into the body), which is the preferred method, and ex vivo (outside the body, where cells are modified and then reintroduced into the patient). Gene therapy involves altering a person's genetic makeup, traditionally by introducing new genes or repairing or replacing faulty genes within the body's cells. However, a new technique, CRISPR, allows us to edit DNA within a cell in vivo. Let's examine this versatile tool in detail (Hahn & Avrahm, 2023).

GENE EDITING

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), the prevailing gene-editing technology, is revolutionizing genetics and health care by providing a powerful tool for the precise manipulation of DNA sequences in patients. It offers new possibilities for disease treatment, diagnostics and research. This gene-editing tool is known for its precision, simplicity and efficiency. It is being applied in various medical fields, including hearing disorders (Xu, Y., & Li, Z., 2020).

Understanding the Mechanism: The CRISPR-Cas9 system, the backbone of CRISPR technology, is a two-part system. The first part is the Cas9 enzyme, which acts as molecular scissors, cutting DNA at specific points. The second part is a guide RNA (gRNA), which acts as a GPS, directing Cas9 to the exact location in the genome that needs editing. CRISPR technology has been adapted to target multiple genetic mutations simultaneously. For instance, a study used CRISPR to target mutations in mice's *Atp2b2* and *Tmc1* genes, showing that this approach could partially restore hearing (Tao, Y. et al., 2023). This unique system enables precise modifications to the DNA of living organisms, allowing for the correction of genetic defects at their source.

CRISPR's Advantages:

1. *Precision and Targeted Correction*: One of the key advantages of CRISPR therapy is that it can directly correct the genetic mutations that cause hearing loss at the DNA level. This is a significant departure from

traditional treatments that often only manage symptoms without addressing the underlying genetic cause. For instance, CRISPR-Cas9 has been successfully used to specifically target and disrupt mutations in genes like Tmc1, which are known to cause progressive hearing loss. This has led to the preservation of hearing function in animal models (Gao et al., 2018; Chien WW., 2018).

2. *Permanent Solutions:* Unlike hearing aids or cochlear implants, which provide symptomatic relief, CRISPR therapy has the potential to offer a long-lasting, if not permanent, solution to genetic hearing loss by correcting the mutation itself. This could reduce the need for ongoing treatments or device maintenance (Fliesler, N., 2019; Chien WW., 2018).
3. *Broad Application Spectrum:* CRISPR's adaptability allows it to target a wide range of genetic mutations associated with hearing loss, including both recessive and dominant forms of the condition. This broad applicability could make it a viable option for many patients who currently have limited treatment options (Yin et al., 2023; Tao Y. et al., 2023).
4. *Safety and Specificity:* By delivering the CRISPR-Cas9 protein directly into the inner ear cells, researchers have improved the specificity of the treatment, potentially reducing the risk of off-target effects that could arise from more systemic delivery methods. This localized approach enhances the safety profile of CRISPR therapy (Gao et al., 2018).
5. *RNA Editing Capabilities:* CRISPR therapy is not limited to DNA editing. CRISPR-Cas13 can target RNA, offering a reversible and potentially safer alternative for modulating gene expression without permanently altering the genome. This could be particularly useful for treating dominant-negative mutations where reducing the expression of the mutant allele might alleviate the condition (Zheng Z. et al., 2022).
6. *Overcoming Limitations of Existing Therapies:* Current treatments like hearing aids and cochlear implants do not cure hearing loss but rather amplify sound or stimulate the auditory nerve directly to improve hearing perception. CRISPR therapy aims to correct the root genetic cause, potentially restoring natural hearing without the need for external devices.
7. *Diagnostic Applications:* CRISPR technology can be adapted for diagnostic purposes, allowing for the precise identification of genetic mutations that cause hearing loss. This capability can lead to earlier and more accurate diagnoses, which are essential for effective treatment planning and management of hearing disorders (Wu, J. et al., 2023; Yin et al., 2023).
8. *Innovative Research Tool:* As a research tool, CRISPR facilitates the exploration of the genetic landscape of hearing loss, helping to uncover new genes involved in auditory function and disorders. This can lead to the discovery of novel therapeutic targets and strategies for preventing or reversing hearing loss.

Audiology clinics have limited options to slow down or reverse genetic deafness. Luckily, CRISPR therapy is a major breakthrough in addressing genetic hearing loss, providing accuracy, the possibility of long-lasting correction, flexibility and enhanced safety. As scientific advancements carry on, CRISPR will surely continue to revolutionize the treatment and diagnosis of genetic hearing loss and overcome the drawbacks of current therapies.

Examples of Gene Therapy

Example 1: Pioneering animal genetic research. The Spns2 tm1a mouse mutant has a faulty Spns2 gene, which causes it to be unable to maintain the local ionic environment of the inner-ear sensory hair cells. This results in a decreased endocochlear potential, a neurological disorder causing irreversible hearing loss.

In this pioneering research, Martelletti et al. (2023) used genetic intervention to reactivate the faulty Spns2 gene and found they could reverse an existing neurologically based hearing loss.

By activating Spns2 gene transcription at different ages after the onset of hearing loss, they discovered a crucial factor in this therapy. The timing of the therapy was critical. The earlier the activation of the Spns2 gene, the more effective the reversal of the hearing impairment was, underscoring the importance of early intervention for this therapy.

This successful study in mice opens possibilities for future gene therapy for reactivating hearing in people with similar hearing loss. That brings us to Example 2, the first demonstration of gene therapy for human hearing loss.

Example 2: The first successful hearing-restoring gene therapy for humans. Autosomal recessive deafness 9, caused by mutations of the OTOF gene, is characterized by congenital or prelingual, severe-to-complete, bilateral hearing loss. Before this study, no treatment was available for this congenital deafness.

This single-arm, single-center trial enrolled six children (aged 10 months–18 years) with severe-to-complete hearing loss and confirmed mutations in both alleles of OTOF and without bilateral cochlear implants. A single injection of AAV1-hOTOF was administered into the cochlea through the round window (Jun Lv, et al., 2024).

The gene expression had a time-release pattern. Five of the six children recovered some hearing over time. At 26 weeks after treatment, they showed an average 40–57 dB improvement in the auditory brainstem response (ABR) thresholds at 0·5–4·0 kHz.

The gene therapy technique used in these studies overcomes a significant challenge presented by large genes, such as OTOF, which exceeds the capacity of the widely used adeno-associated virus (AAV) vectors. Researchers addressed this by dividing the OTOF gene into two, encapsulating the halves into separate viruses, and then injecting a mixture with both halves into the cochlea. This innovative approach allowed the cellular machinery to assemble the complete protein, restoring the cells' ability to transmit signals to the brain.

The children were cochlear implant candidates, but after acquiring enough hearing from gene therapy, they were no longer eligible for implants. They will be treated with hearing aids. Researchers are following the patients for five years to see if their hearing continues to improve.

Successful OTOF gene therapy treatments are continually emerging, underscoring the importance of pediatric gene therapy. Auditory Insights has published a summary of these studies at https://auditoryinsight.com/wp-content/uploads/securepdfs/2024/02/Gene-Therapy-Clinical-Trials-Results.pdf.

Potential Benefits of Using Gene Therapy to Treat Genetic Disorders in Embryonic Humans

Intrauterine Fetal Gene Therapy

As innovative and promising as the above therapies are, intrauterine fetal gene therapy (IUGT) offers even more promise. Peddi and colleagues (Peddi et al., 2022) have written a comprehensive review that offers an overview of the current knowledge in the field of prenatal gene therapy, as well as potential future research avenues. It is recommended reading. Here are some of intrauterine fetal gene therapy's distinctive benefits:

- **Less Invasive Approach**

IUGT provides minimally invasive approaches to preventing genetic disorders by releasing vectors into the embryonic fluids.

- **Prevention and Cure of Genetic Disorders**

IUGT can prevent or cure genetic diseases by correcting gene mutations in embryos, giving individuals a chance at a healthy life beginning at birth.

- **Elimination of Hereditary Disorders**

Germ-line gene therapy, which targets reproductive cells, has the potential to permanently remove hereditary disorders from a family line.

- **Reduction in Health Care Costs**

By preventing genetic disorders before they manifest, IUGT could significantly reduce the long-term health care costs associated with hospital stays, treatments and lifelong care.

Peddi and colleagues also point out the following aspects of fetal development, which make treatment delivery more efficient, safe and long-lasting:

» *Small fetal size:* Due to the cost and manufacturing constraints associated with gene treatments, the small fetal size allows for smaller, less expensive dosing.

» *Accessible proliferating progenitor cells:* In the fetus, specific body compartments and cells are more accessible, allowing systemic gene therapy to reach a wider range of cell types. Progenitor cells are abundant and generally proliferative in the fetus, increasing the likelihood of propagating a therapeutic correction or gene integration.

» *Tolerogenic fetal immune system:* Immune reactions to transgenes and vectors may restrict postnatal gene treatments. However, prenatal delivery studies show that due to the tolerogenic fetal immune system, there is no immunological response to viral transgenes, including Cas9.

IUGT provides minimally invasive approaches to preventing genetic disorders. IUGTs are the future of fetal and neonatal medicine to improve quality of life and potentially cure monogenetic disorders before irreversible pathology occurs.

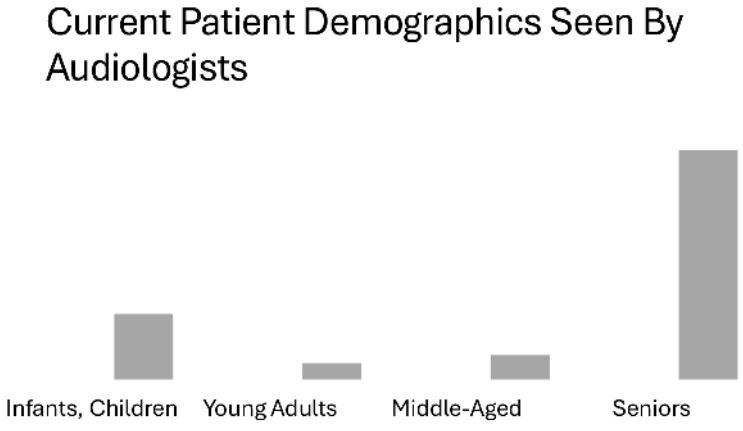
As a result, there are increasing calls to adopt a simultaneous genetic hearing loss screen to the current neonatal health screening guidelines (Pei et al., 2022). Suppose a screening test indicates a possible problem—or the parents' age, family history or medical history puts the baby at increased risk of having a genetic problem. An invasive prenatal diagnostic test and IUGT might be considered in that case. Imagine the benefits of this approach combined with newborn hearing screening to start an otherwise deaf child's life with hearing.

Ethical and Cultural Considerations

Ninety to 95% of deaf children are born to hearing parents (Mitchell et al., 2004), many of whom would like to make hearing possible for their children. For them, this is a miracle; they can choose gene therapy. However, we must be sensitive to the idea that some deaf parents prefer deaf children and, in both cases, support the parents' decision. This ethical mindfulness is crucial for ensuring that treatments are developed in a way that respects patient autonomy and diversity (DesGeorges, J., 2016).

Resulting Patient Demographic Shifts

Most therapies work best when they are started as early as possible. The gene therapy examples discussed above confirm that gene therapies also conform to this "earlier is better" rule. In addition to the IUGT advantages listed above, it is the earliest possible therapy. As a result, we can expect an increase in the number of pediatric and fetal patients receiving treatment.



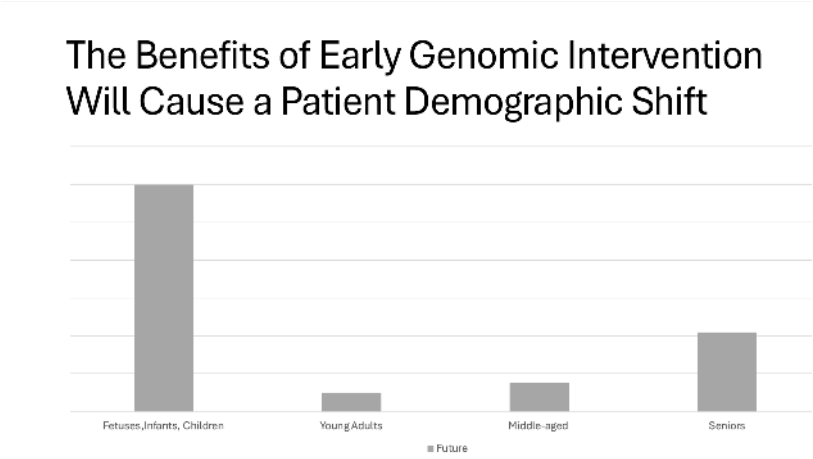
Currently, newborn hearing screening demands

a small cadre of pediatric audiologists.

Most audiologists treat seniors, where the demand is greatest.

Still, because gene therapies work best in younger patients, we must plan for an increased emphasis on pediatric patients and inter-uterine fetal gene therapies.

To the extent gene therapy is successful, IUGT patients may experience a lifetime without congenital sensorineural hearing loss, reducing the demand from older patients.



Traditional Audiology Still Has a Role

Gene therapy will not entirely replace hearing aids and cochlear implants—at least not for a generation or two. Because gene therapy works best at younger ages, the boomers will still need and expect traditional therapies while we shift toward younger genome therapy patients. The baby boomer generation's peak is reaching 65 years of age—4.1 million Americans are reaching age 65 annually. Many of those at 65 still have 10, 20 or even 30 years ahead as life expectancy increases. Additionally, the second half of this large boomer generation is still under 65.

Gene therapies are still in their infancy and need time to be perfected. Gene therapy has shown that it is not always a complete solution or cure for humans (Jun Lv et al., 2024) and animals (Martelletti et al., 2023). For instance, in the case of OTO-F-treated children, while they no longer required cochlear implants, they still needed hearing aids. This highlights the imperfections of gene therapy. Not all gene therapies will immediately work perfectly or last a lifetime. This is when the collaboration between audiologists and geneticists becomes crucial. It is our future! Together, we must devise successful new treatments for patients who have undergone gene therapy. Some of these treatments will be traditional, some will be modifications of traditional treatments, and some will be innovative solutions that we can't yet envision.

Because of the rapid development and success of gene therapy, we surely must now plan for the shift of our expertise to younger patients and a growing partnership with genomics. Those forces will dominate the future for today's and tomorrow's audiology students. To allow us to make this shift, we must use audiology extenders and AI to care for nonprescription patients and to free us to work with geneticists to treat more complicated patients requiring prescription care. Audiologists who participate in precision medicine and actively collaborate with geneticists will thrive.

Soon, audiologists will work in a precision medicine-based health care world, using advanced machine intelligence on powerful computers, personalized by genomics, and massive data sets.

Now is the time to prepare for this unstoppable, breathtaking transformation of hearing health care.

A CALL TO ACTION

When the winds of change blow, some people build walls; others build windmills.

The integration of precision medicine and genomics into audiology promises to enhance the diagnosis, treatment and management of hearing loss. This exciting integration involves several strategic steps and considerations to ensure effective implementation.

By adopting these strategies, audiologists can effectively stay up to date with the rapidly evolving field of precision medicine and genomics, ensuring that they are well-equipped to provide the most advanced and personalized care to their patients.

How to Build Windmills: 13 Key Steps for Implementation

1. *Increased Training in Precision Medicine, Genetics and Genomics:* Audiologists urgently need more training in genetics and genomics to integrate these insights into clinical practice effectively. This training should cover genetic testing, interpretation of genetic results and the implications of genetic findings for treatment strategies. We must also seek additional education and training in areas relevant to precision medicine, such as data analysis and artificial intelligence.
   Engaging in discussions and attending presentations can provide insights into how precision medicine is being integrated into audiological practice. Attending workshops, enrolling in relevant courses and participating in professional development programs and conferences on these topics are crucial, while conferences offer opportunities to network with leading audiology, genetics and precision medicine experts. Clinics must budget support for staff to attend these educational opportunities.
2. *Genetic Testing and Counseling:* We must be prepared to provide or offer genetic counseling to patients and their families about the implications of genetic findings, including the risks of inherited hearing loss and the potential for targeted interventions. Audiologists should establish a referral system where patients

with suspected genetic-related hearing loss are promptly referred to genetic counselors. This ensures that patients receive comprehensive genetic counseling and testing, which can significantly influence the management and treatment of hearing loss.

3. *Post-Therapy Treatment:* After gene therapy, audiologists will be needed to monitor and treat a variety of therapy-treated patients. Audiologists and genetic counselors can co-manage patients, especially in complex cases where the hearing loss may be part of a broader genetic syndrome. They can participate in joint professional development programs to stay updated on the latest advancements in genetics and audiology. This approach ensures that all aspects of the patient's condition are addressed comprehensively.
4. *Interdisciplinary Training and Collaboration:* Precision medicine requires creating new partnerships with scientists in a wide range of specialties, as well as people from the patient advocacy community, universities, pharmaceutical companies and others. This will involve participating in interdisciplinary teams, attending interdisciplinary meetings or developing collaborative relationships with professionals in other fields.
5. *Adopting Advanced Technologies:* We must strive to adopt and integrate advanced technologies, such as genetic testing tools and data analysis software, as they become available. We must also develop expertise in implementing computational audiology tools that use artificial intelligence and machine learning to analyze genetic data and predict treatment outcomes. These tools can help identify potential candidate genes for hearing loss and refine diagnostic and treatment processes. Investment and training will be required.
6. *Adopt Standardized Datasets:* Because audiology data can be found in a wide range of formats and structures, data preprocessing is often necessary to extract meaning and ensure data usability in the precision medicine system. We must establish systems and routines to seamlessly integrate correctly formatted and standardized hearing health care data into the precision medicine database system regularly.
7. *Electronic Health Records (EHRs):* EHRs are the vehicle for using patient data across professions. With primary care physicians embracing advanced EHRs such as EPIC, initially utilized in hospitals for seamless information exchange between various platforms and patients, it is crucial for audiology clinics to adopt EHR systems that are compatible with precision medicine databases and encourage universal data access. This adoption will enhance the availability of genetic data for continuous patient management and streamline the creation of personalized treatment plans.
8. *Patient-Centered Approaches:* It's essential that we routinely develop personalized treatment plans that consider the patient's genetic profile, lifestyle and environmental factors. We also should educate patients about the role of genetics in hearing health and involve them in decision-making processes regarding their treatment options. Engaging patients in this way can lead to better compliance and satisfaction with the treatment outcomes.
9. *HHC Device Health Monitors:* Audiologists should actively promote the use of hearing devices as health monitors. This not only underscores the vital role they play in providing real-time data for precision medicine but also highlights the potential of these devices to revolutionize health care data management (Nielsen, 2024).
10. *Research and Development:* Engaging in or supporting research initiatives that explore new diagnostic tools and treatments in precision medicine can contribute to its advancement and ensure that audiologists are at the forefront of new treatment modalities and technologies.
11. *Address Ethical Issues:* AI, precision medicine and genomics present a new, complex set of ethical and

security issues. Regularly seek ethical training, consult with ethicists, develop ethical guides for your practice and follow best practices for security issues.

12. *Navigating Reimbursement and Financial Challenges:* Work to understand the reimbursement landscape for precision medicine by advocating for coverage, hiring reimbursement consultants and attending workshops.
13. *Cost and Accessibility:* Using new technologies and innovations, we must strive to transform hearing health care to be increasingly affordable and accessible, including addressing the cost of genetic tests and ensuring equitable access to genomic medicine resources.

The integration of precision medicine and genomics into audiology requires a structured approach involving education, technological integration, ethical considerations and patient-centered care. By embracing these elements, audiology can significantly improve the precision and effectiveness of hearing health care, offering patients more tailored and more effective interventions for various forms of hearing loss.

Starting now, we need to promote and establish a roadmap for incorporating precision medicine and genomics into hearing health care. Neglecting this pressing opportunity could result in others being responsible for diagnosing and treating hearing disorders as precision medicine and genomics become dominant forces in the medical field.

SUMMARY

The assumptions that have traditionally underpinned audiology, dictating decisions about what to do, who does it and what not to do, are no longer aligned with our new AI-enabled, precision medicine-driven reality. This misalignment underscores the necessity of reevaluating and updating our practices.

The strong human inclination to believe that tomorrow will be similar to today is rooted in the fact that it is usually accurate. But not right now!

The fields of genAI, genomics, precision medicine and computer-driven big data analysis/systems are all experiencing simultaneous growth and advancement. With this innovation and technology integration, audiologists are offered a range of new, improved and competitive options.

Precision medicine amplifies audiologists' capabilities and reach by empowering them to analyze vast datasets, unearth previously inaccessible relevant information and leverage that information for personalized patient diagnosis and treatment decisions. The transformative potential of precision medicine in how we deliver prescription hearing health care cannot be overstated, underscoring the urgency of its adoption.

We should prioritize leaving behind outdated practices from the 1900s and instead consider assigning them to audiology extenders. It is crucial to embrace modern diagnostic and treatment methods that take advantage of the rapidly advancing opportunities offered by precision medicine and genomics. This will enable us to diagnose and treat patients more effectively. Importantly, this approach offers a promising and viable strategy for the future of audiology, filled with hope and optimism for our patients and profession.

EPILOGUE

THE NEED FOR LEADERSHIP

"I think the fundamental role of a leader is to look for ways to shape the decades ahead, not just react to the present, and to help others accept the discomfort of disruptions to the status quo."—Indra Nooyi, Former Chairwoman and CEO of PepsiCo

The introduction clearly states that tomorrow will be different from today. Doing what was done before is no longer a formula for success. The rate of change is faster now than ever before, and professions are struggling to keep up with the rapid pace of technological innovation.

Significant changes are increasingly essential to thrive and compete in this volatile landscape. Flourishing in this whirlwind of change necessitates strong leadership. As Indra Nooyi has emphasized, leadership's fundamental role entails effectively dealing with change.

More change always demands more leadership!

We must seek out people at all levels in audiology with leadership potential and expose them to career experiences designed to develop that potential. Today's transformation of health care presents numerous opportunities for this development. We must grow a professional culture that values more strong leadership and constantly creates it.

Leading a profession to a constructive transformation begins by developing a vision of the future and strategies for producing the changes needed to achieve that vision. In this and my previous paper (Nielsen, 2024), I have attempted to suggest what that vision might look like and some strategies to go in that direction. As a professional, your responsibility is to create your vision of the future of audiology and then communicate it to others to align all members of the profession, including clinical practice, research and professional education, around a feasible way to obtain a new, broader and very different common vision.

To achieve success, one must possess the courage to take risks, the persistence to overcome obstacles and the ability to think strategically by gathering and analyzing extensive data, as well as identifying patterns, relationships and connections that provide explanations.

Accomplishing such a challenging task demands a significant amount of time and effort. It must be prioritized, not treated as a secondary task. It's time to take action! We need you to be involved in the transformation of hearing health care. I leave you with this thought from John F. Kennedy:

"It is time for a new generation of leadership to cope with new problems and new opportunities. For there is a new world to be won."

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Don Nielsen serves as the Audiology University Advisor at Fuel Medical Group. He started his professional journey as a fundamental scientist, studying the intricate mechanics of the inner ear and collaborating with William A. Yost to publish the highly successful introductory textbook “Fundamentals of Hearing: An Introduction.” He was a member of the leadership teams in the ENT department at Henry Ford Hospital and the House Ear Institute. As the head of research, he successfully led transformative initiatives for both. Dr. Nielsen has held various prestigious positions in the field of audiology, including Director of the Central Institute for the Deaf, Chair of the Speech and Hearing Department at Washington University, St. Louis, Director of the Audiology Clinic and Translational Research at Northwestern University’s Communication Sciences Department, and President of the Association for Research in Otolaryngology.


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