A STRUCTURED ARGUMENT FOR THE USE OF AI IN PRECISION MEDICINE

SWATI MISHRA
TERM PROJECT
CS 781

TABLE OF CONTENTS

TABLE OF FIGURES

THESIS

Artificial Intelligence can and should be used to significantly enhance the efficiency and accessibility of Precision Medicine by addressing the challenges that deter its extensive application in healthcare.

INTRODUCTION

Understanding AI's role in Precision Medicine begins with understanding what Precision Medicine is and the challenges in making it accessible to most patients. Precision Medicine uses varied data about a patient like their family history, environmental factors, remote devices, genomic data, biomarkers, etc, to customize treatment. This also includes patient stratification and risk prediction.

The availability of true precision medicine is limited, especially as most physicians don't have these resources available for every patient. While this has been supported by current health technology (EHR, drug alerts, genetic markers), AI can improve speed and availability by integrating and analyzing these separate data sets into useful information about the patient. There is a **bottleneck**, and the vast health data, even when available, cannot be fully utilized, and this is where AI comes in.

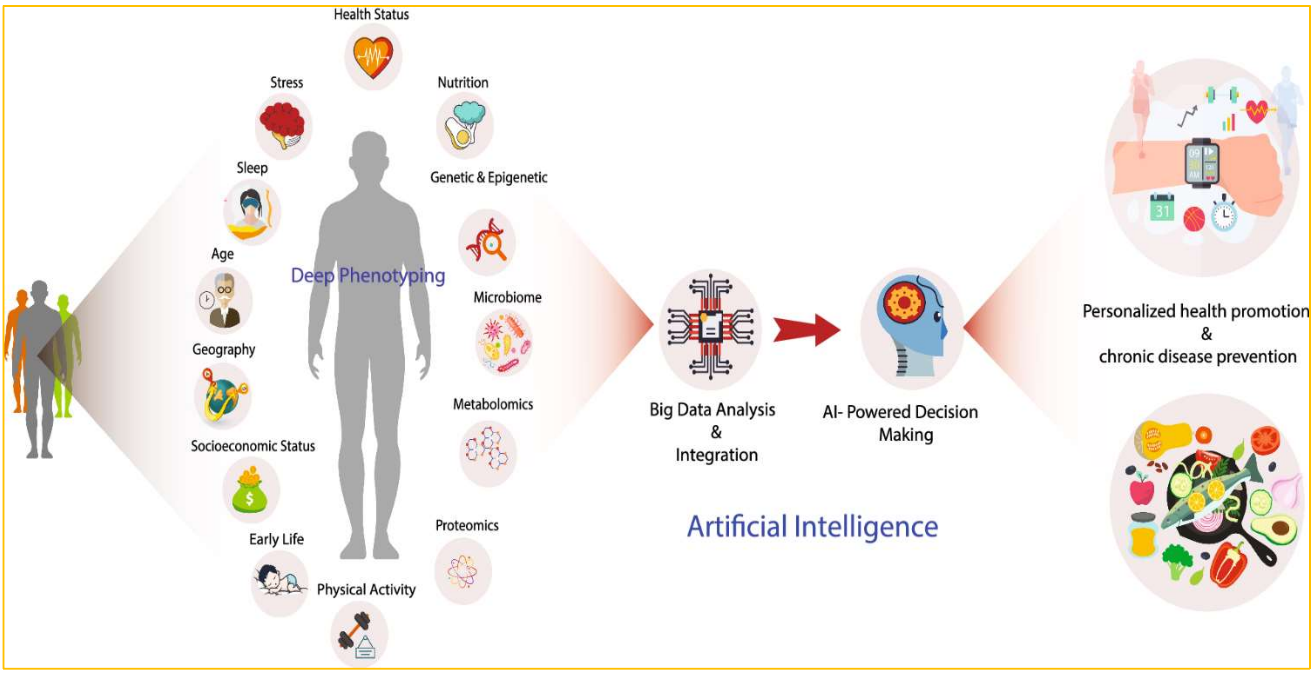

Figure 1. How AI can drive Precision Medicine. (Subramaniam, 2020)

PRECISION MEDICINE

The idea of Precision Medicine has existed since the late 90s, but it became mainstream after two decades in 2010-11 (Jørgensen, 2019). In 2015, President Obama launched the **Precision Medicine Initiative** which defined Precision Medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." Precision Medicine is important because most of our treatments and drugs are based on what the majority of people respond to, and so, many are receiving treatment that is the best for many others, but not for them. (MedlinePlus, NLM)

Precision Medicine now is envisioned as a holistic approach that includes clinical findings, data from digital health devices, imaging data, omics data (genomics, proteomics, etc.), and health technology. **Two** major reasons that **facilitate** the modern development of the concept and actual usability of **Precision Medicine** are – a) the use of EMRs and Health Tech that makes data available digitally, for storage, communication, and analysis, and b) the advances and reduced cost in omics technologies like DNA sequencing/ genomics, proteomics, etc. (Ginsburg & Phillips, 2018).

Precision Medicine is currently being explored for cancer, cardiovascular diseases, metabolic diseases, neurodevelopmental disorders (NDD), and rare diseases. Diseases with known genetic markers and biomarkers have the most potential for using Precision Medicine to improve patient outcomes.

ARTIFICIAL INTELLIGENCE

Artificial Intelligence is a broad field, and only certain parts are relevant to healthcare, especially Precision Medicine. Artificial intelligence, or AI, enables computers and machines to simulate human intelligence and problem-solving capabilities (IBM.com).

All AI currently is Narrow AI, which means AI that is trained to perform a narrow task like creating text-based chat (IBM.com, 2023). AI models work on algorithms and can be trained to not only perform certain tasks but also learn about these tasks by themselves. This is machine learning (ML - supervised or semi-supervised), and an advanced form of this is Deep Learning (DL) that includes Neural Networks like Deep NN, Convolutional NN, Recurrent NN, etc. DL is mostly unsupervised or semi-supervised learning. The learning requires instructions and algorithms, and very importantly a dataset on which to train. Generative AI uses DNN and can create its own output like text, images, and audio (IBM.com, 2023, and HealthITAnalytics.com).

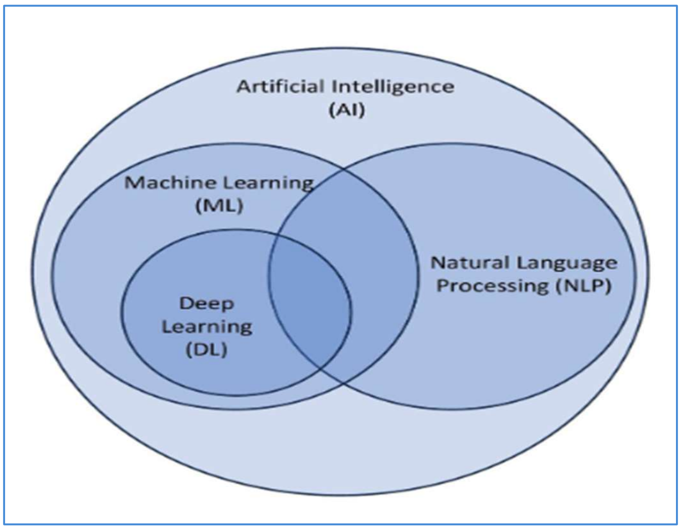

Figure 2. An Overview of AI's Subcategories

THE INTERSECTION OF PRECISION MEDICINE AND AI

The role of AI in healthcare is a reality in some fields, yet only a concept in others. This diagram shows where Precision Medicine and AI are at, but we need to see not only Precision Medicine but also fields that will impact Precision Medicine like Predictive Modelling and Medical Imaging.

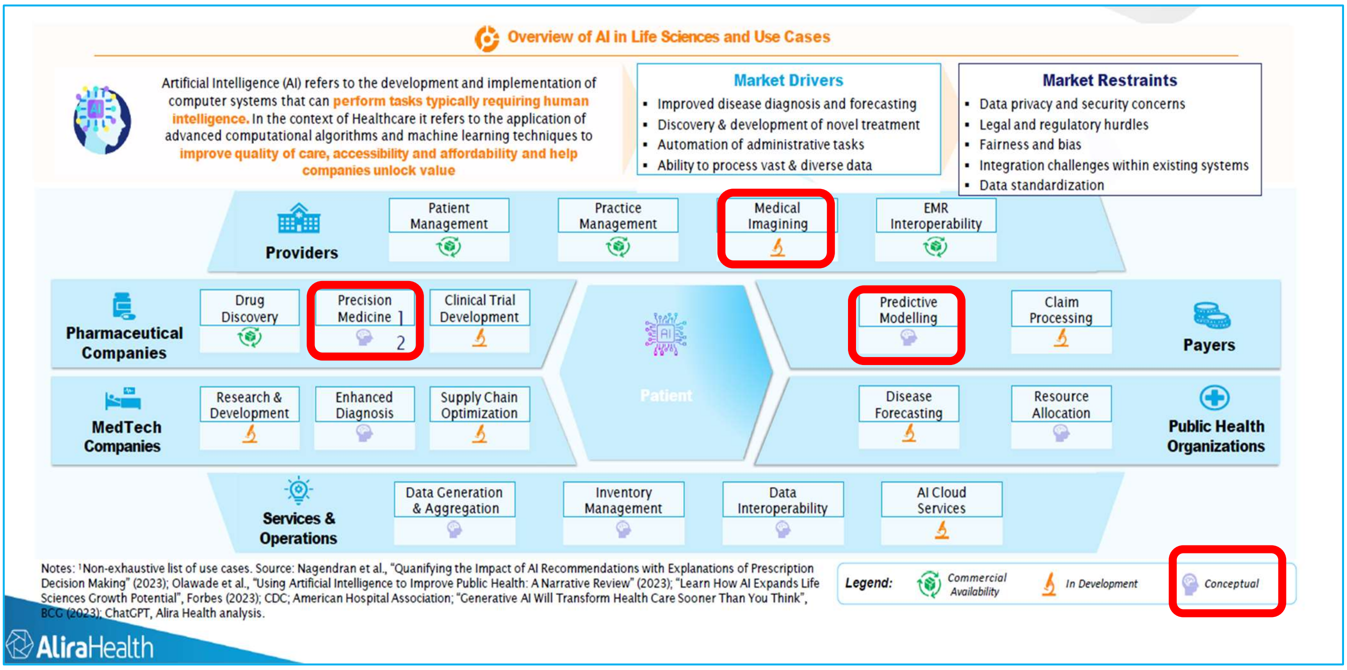

Figure 3. AI in Life Sciences. Picture from Michael Levinger Module 4 lecture.

Precision Medicine uses AI to digest the vast genomic, behavioral, and environmental data for risk prediction, drug dosage adjustment, and analyzing all available data about a patient to recommend tailored treatment. Understandably, the amount of information that is considered ranges from family history to molecular makeup (omics), and for a physician to process this and derive any useful information, without AI's help, is near impossible.

LITERATURE REVIEW AND UNDERSTANDING OF THE CURRENT SCENARIO OF AI USE CASES IN PRECISION MEDICINE

The literature about AI in healthcare is highly inconsistent (as is usual for new topics with a sudden increase in articles and writings), and the use of AI in Precision Medicine is even more so. Most studies are focused on one disease (Alzheimer's, or colon cancer), or very high-level potential uses, making the categorization and sequence of topics difficult. Here, we will start with Precision Medicine, then AI in Precision Medicine, followed by more specific case studies as examples.

PRECISION MEDICINE, AI, AND HEALTH TECHNOLOGY

Precision Medicine as described earlier is the treatment of a patient based on multiple factors, like family history, environment, genomics, and other omics, etc. Already Precision Medicine is supported by existing health tech like EHRs, and in the future will be supported by AI-supported EHRs that contain more than the patient's clinical history.

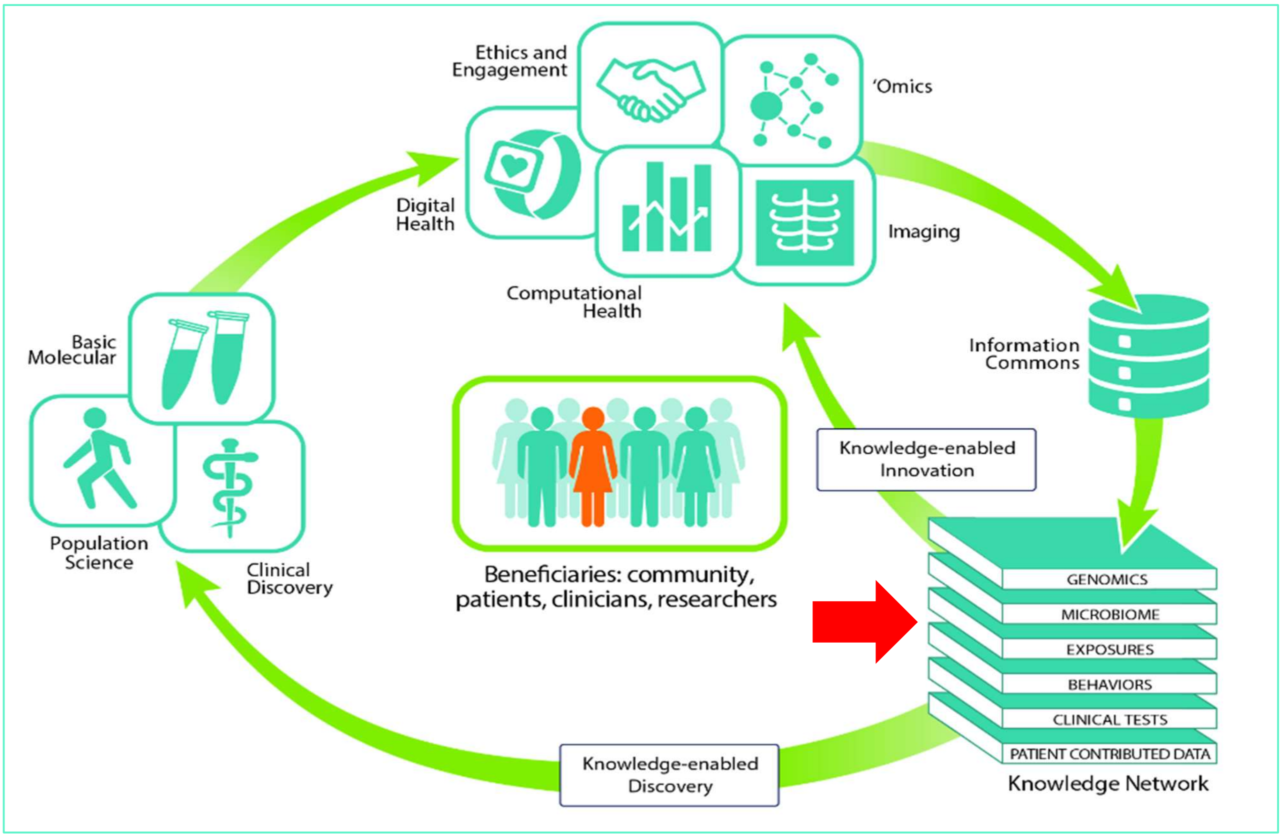

Figure 4. Precision medicine, its data sources (red arrow), its dependency on health tech, and its beneficiaries. (UCSF.edu)

The above diagram makes it amply clear that existing tech is needed for Precision Medicine, and the advancements in omics, imaging, and electronic records are vital to Precision Medicine. **Omics advancements** refer to understanding not only genome but also various other omes (Fig 5) that are disturbed during various disease processes and can be both diagnostic or risk predictors. Their **data is vast and needs high computation, processing, and analysis to yield informative results**. The potential of AI in their analysis is already recognized (Sethi, 2023)

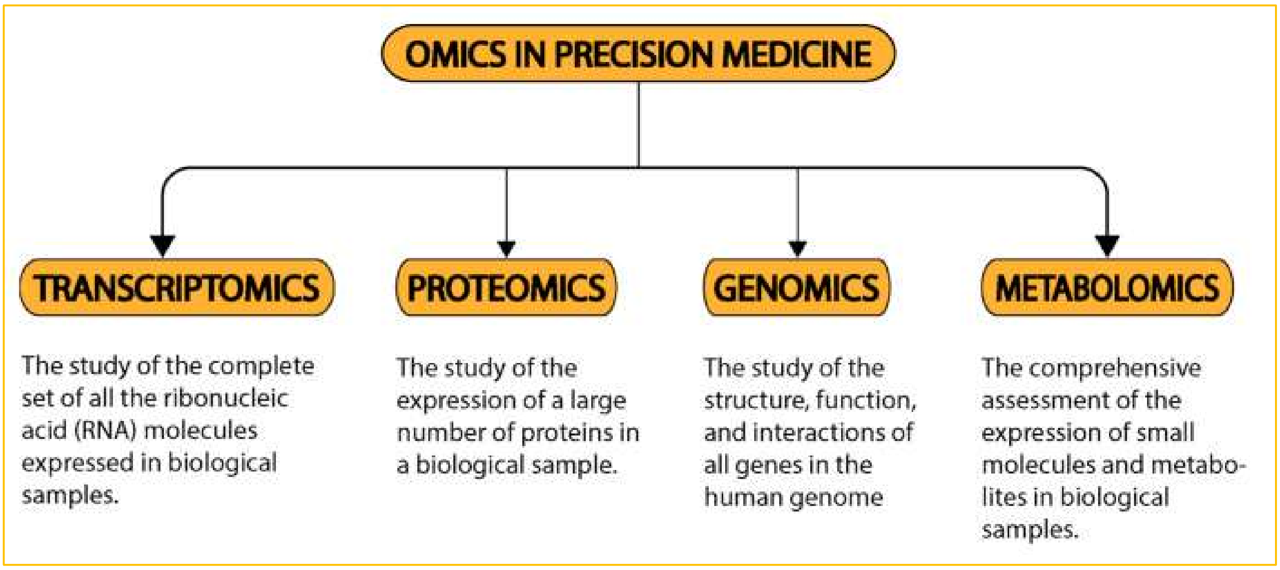

Figure 5. Various omics in precision medicine. (Aronson, 2015)

Understanding how the current Health IT supports Precision Medicine (Fig 6) will help to realize exactly what areas can AI be used to make Precision Medicine faster and more accessible. **Data collecting, cleaning, and ANALYSIS** to create a personalized treatment plan, or to predict risk, seem to be the main focus areas, that can be improved significantly by AI.

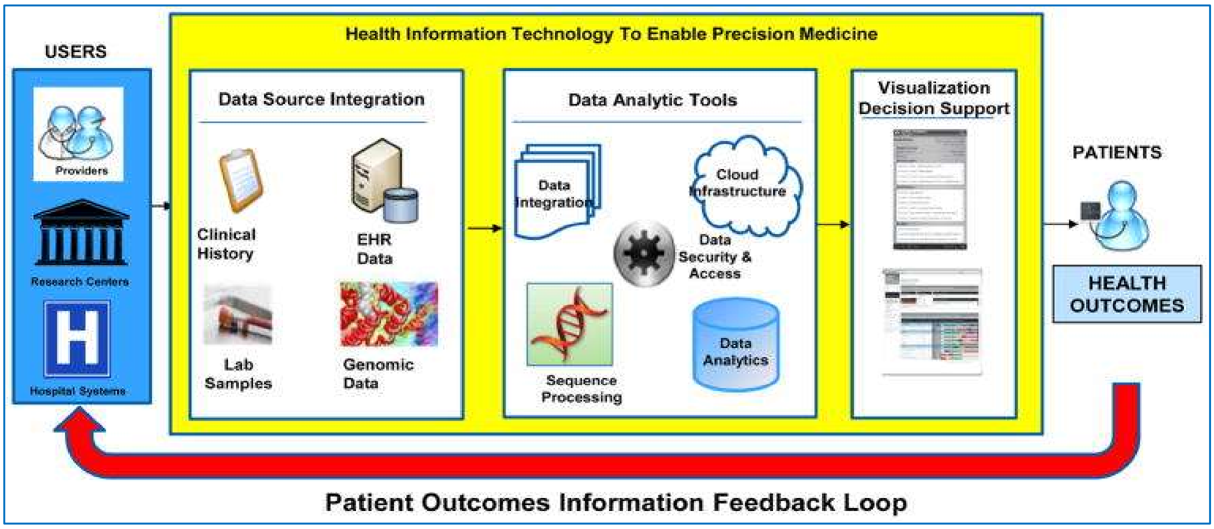

Figure 6. Health IT and Precision Medicine. (National Academies Press, 2015)

The two important aspects where AI will have a significant impact are DATA INTEGRATION and DATA ANALYSIS (Big Data). The output can be **patient stratification, risk predictions, early diagnosis, and tailored treatment.** The main topics that are relevant to AI's role in Precision Medicine are – **Predictive modeling, Data analysis, Machine Learning models and their use, and Natural Language Processing**. This can be further improved by integrating clinical trial data and drug discoveries. The potential to integrate and produce information is vast, but as of now, they are done as isolated cases.

MACHINE LEARNING FOR PRECISION MEDICINE – DATA INTEGRATION, ANALYSIS, AND PREDICTIVE MODELING

The challenge of taking a patient's imaging history, family history, clinical history, genome sequence, and other biomarkers, and then analyzing them in correlation with each other to arrive at a risk factor or diagnosis, is a near-impossible task. Physicians will usually only ask for certain known genes or biomarkers once a patient presents with symptoms or has a family history. But using ML, a lot of this data can be digested and turned into useful information. ML models can be integrated with disease-specific CDSS, to provide a precision health recommendation. Here are some important points from the current literature.

A) DATA FUSION AND ANALYSIS (ML, PREDICTIVE MODELING)

The health data from various sources are fused (data fusion) for analysis and predictive modeling, to create an information state, but this data is disparate, from images to clinical notes to DNA sequences. This fused data is then run through algorithms It can be fused at 3 levels –

Early fusion – This includes fusion of source data like images with EHR, or EHR with genotype. Examples include fusing MRI, FDG-PET, cerebral spinal fluid, and genetic information to predict mild cognitive impairment (Kim and Lee, 2018); Imaging, EHR, and genomic data; EHR and clinical notes, etc. (Kline, 2022).

Intermediate fusion – Source data are categorized and processed, then merged. Examples include merging a) history, lab tests, and symptoms and using MLP (Multilayer perceptron) for clinical data, and Convoluted Neural Networks (CNN) for imaging data, then using them to predict stroke for that patient. The two sets – clinical data and images were separately processed, and later fused. (Zihni, 2020)

Late fusion – Not common, different sources are processed and algorithms applied separately till the final product, then fused using CNN or other DL algorithm, etc.

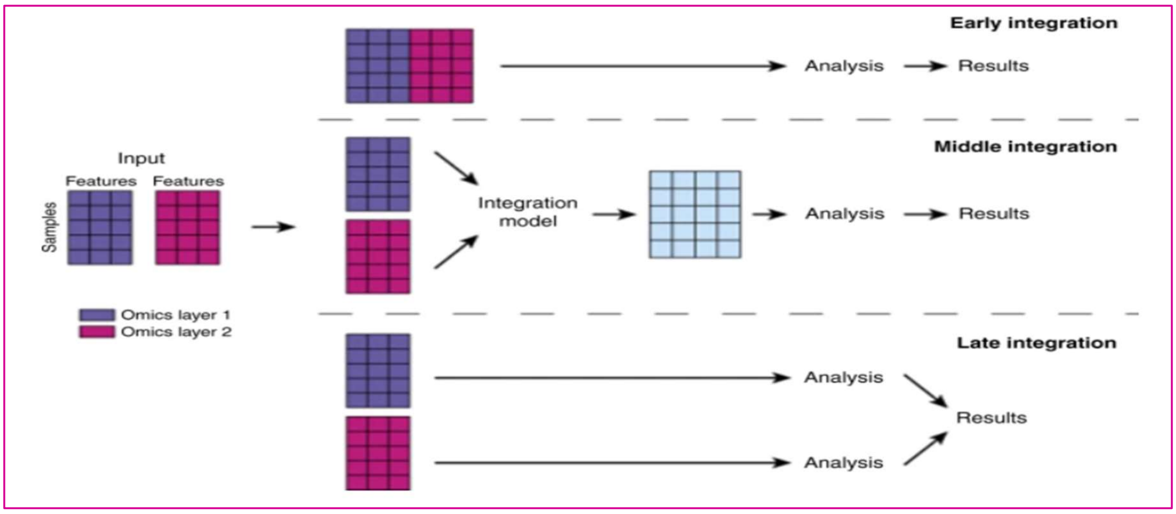

Figure 7. An example of different levels of data fusion/ integration, for omics data. (Cai, 2022)

This diagram (Fig 8) captures the Precision Medicine data sources and their transformations quite well. The main known use of this data fusion (in healthcare) right now is prediction and as more modalities are included (EHR, imaging, genomic, proteomic, history, behavior, environment) the potential in precision medicine could be tremendous.

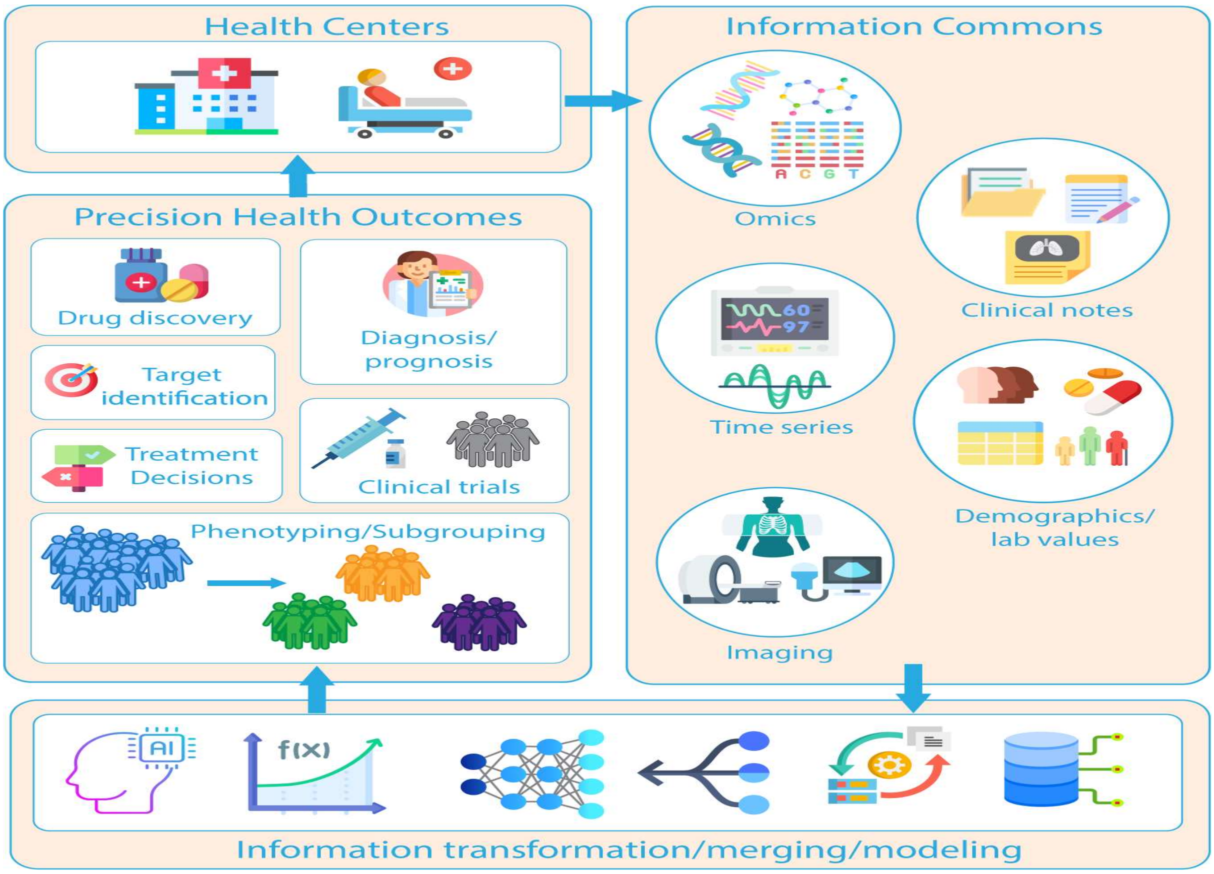

Figure 8. Data flow and transformation for Precision Medicine with ML algorithms. (Kline, 2020)

B) COMMON ML ALGORITHMS CURRENTLY IN USE FOR PRECISION MEDICINE

Some ML algorithms are more common in healthcare data analysis and predictive modeling, the most common ones are Support Vector Machine (SVM), Random Forest (RF), Extreme Gradient Boosting XGBoost, Decision Tree(DT), and Logistics Regression (LR). SVM, RF, and XGBoost are common in precision medicine. (Vadapalli, 2022)

Support Vector Machine (SVM) is a machine learning algorithm used for linear or nonlinear classification, regression, and even outlier detection tasks. They can be used for text classification, image classification, spam detection, handwriting identification, gene expression analysis, face detection, and anomaly detection. (Geeksforgeeks.org)

Random Forest is an ML algorithm that combines the output of many decision trees to reach a single result. Each decision tree in the ensemble is comprised of a data sample drawn from a training set. RF is better at handling regression and classification and identifying a variable's importance or contribution to the output. The downside is it is complex and time and resource-consuming. (IBM.com)

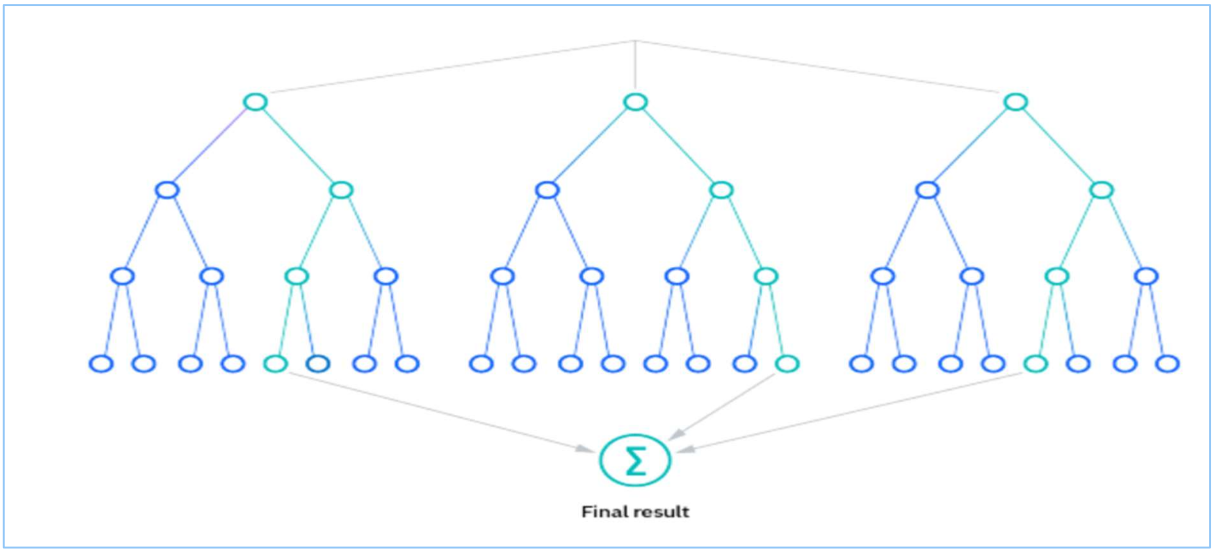

Figure 9. Random Forest schema. (IBM.com)

XGBoost is a scalable, distributed, and gradient-boosted decision tree. This also combines multiple decision trees, like RF, but differently, to arrive at the output. XGBoost is very resource-intensive, and a regular CPU is not enough, a GPU (Graphic Processing Unit) is required. (Nvidia.com)

NATURAL LANGUAGE PROCESSING (NLP) IN PRECISION MEDICINE

NLP is the subset of AI that enables devices or software to perform tasks like –

- Translate text from one language to another
- Respond to typed or spoken commands
- Recognize or authenticate users based on voice
- Summarize large volumes of text
- Assess the intent or sentiment of text or speech
- Generate text or graphics or other content on demand

NLP works using many methods like 'Word sense disambiguation (understanding the meaning of a word in the context), Named Entity recognition (identifying names, places, etc,), Sentiment Analysis, and others. (IBM.com)

Currently, in Precision Medicine NLP has one major potential use – reading papers and clinical trial results and creating data for analysis that in turn can be used for patients. The amount of health data being published is huge, and including the latest knowledge/ protocols for patients as decision support is exactly what Precision Medicine is. Machine reading of articles can help reduce the knowledge bottleneck, and make that data swiftly available for use in medicine. (Poon, 2021, Microsoft Research at NLP summit)

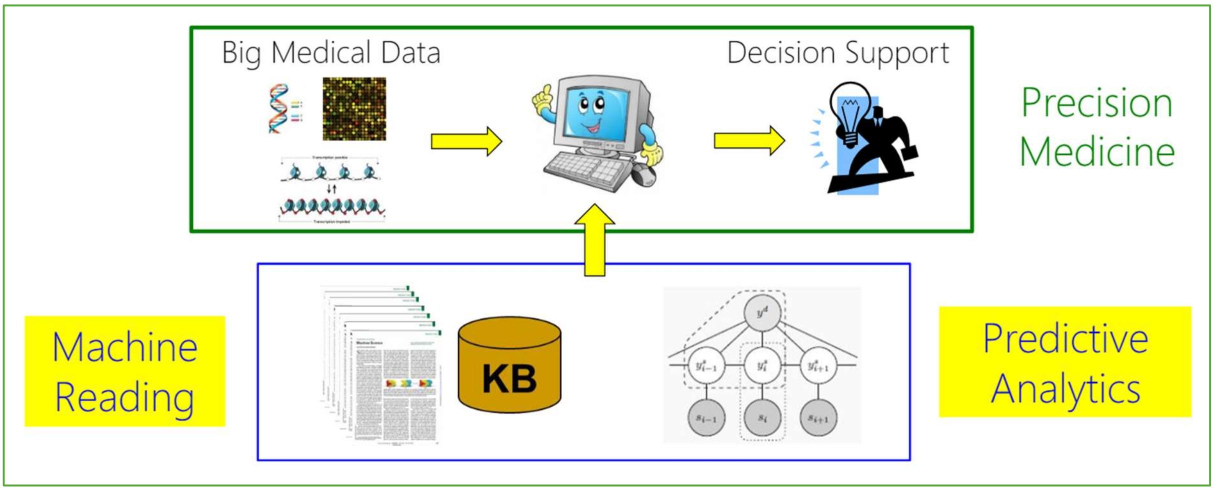

Figure 10. NLP for machine reading of papers/ articles. (Microsoft research). KB = Knowledge Bottleneck due to too many articles.

EXAMPLES OF AI IN PRECISION MEDICINE

1. “A machine learning approach to integrate big data for precision medicine in Acute Myeloid Leukemia” (Lee, 2018)

Cancer Genome Project (CGP) and Cancer Cell Line Encyclopedia (CCLE) have tested certain cell lines for their sensitivity to drugs. For AML, they have data of only 14 cell lines. Lee et al. used a new framework with an ML algorithm - MERGE (mutation, expression hubs, known regulators, genomic CNV, and methylation). It identified reliable gene expression markers by integrating multi-omic prior information. MERGE algorithm also iteratively learns the weights and the degree of impact that genes’ marker potentials have on observed gene-drug associations (for chemotherapy). They found SMARCA4 as a potential biological marker. High expression of SMARCA4 appeared to be sensitive to topoisomerase II inhibitors, mitoxantrone, and etoposide in AML.

There are many examples of **precision oncology** using AI and ML, and the core is – to identify new genes that may be associated with cancer or identify the drug sensitivity of these cells for potential cancer therapies.

2. “A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the Blarcamesine (ANAVEX2-73) Phase 2a clinical study” (Hampel, 2020)

Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder. SIGMA -1 Receptor (SIGMAR 1) activation can reduce the disease progression, so a drug called **Blarcamesine, a SIGMAR 1 activator is being studied for AD**. Hampel et al used an unsupervised algorithm where Formal Concept Analysis (FCA) was integrated with a Knowledge Extraction and Management (KEM) environment using genomic (Variant and Gene expression), pharmacological, and clinical data. This AI algorithm helped to **identify two DNA variants that responded to Blarcamesine** and the relation of patient improvement with drug dosage (when these genomic markers were present. The amount of data and correlations processed could only be done by AI.

AI also shows promise in precision medicine for Neurodevelopmental disorders (NDDs).

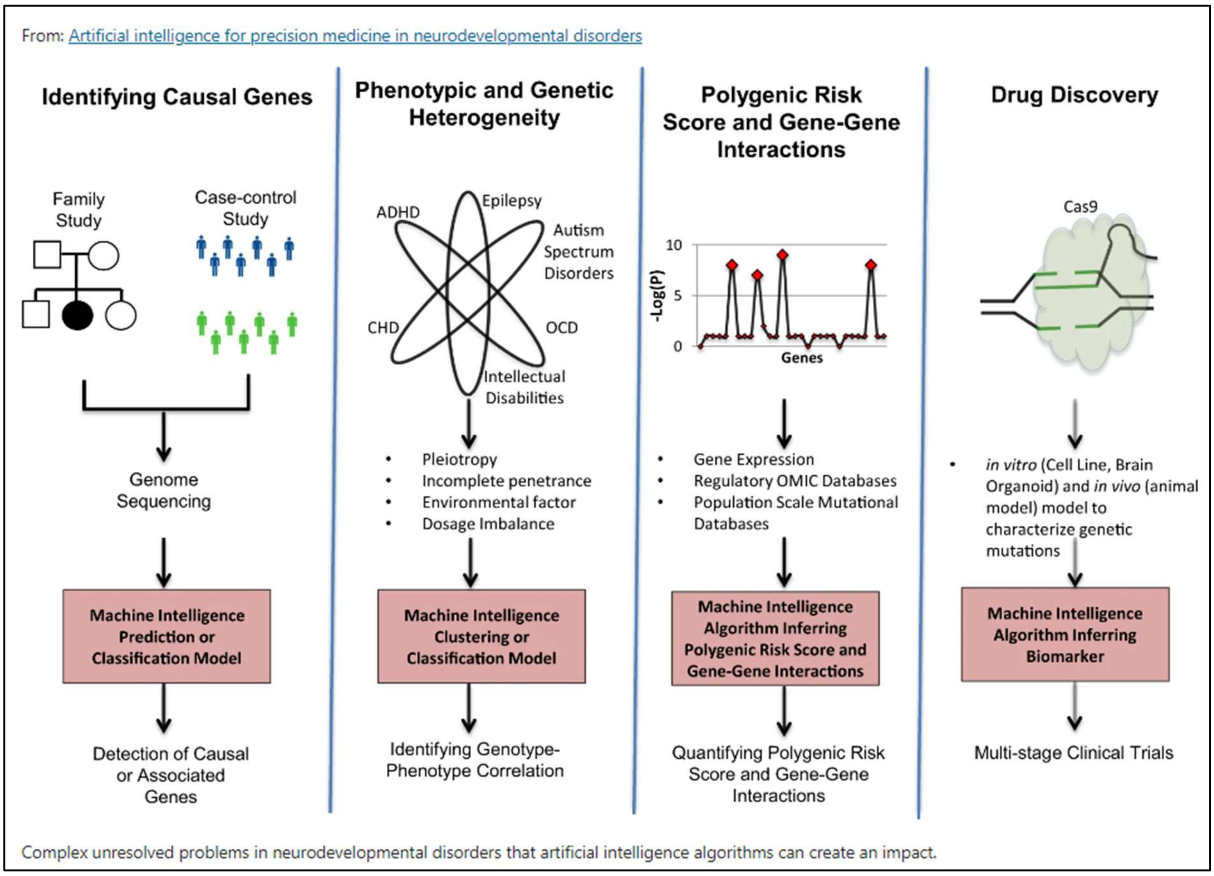

Figure 11. AI's potential use cases for Precision Medicine in NDDs. (M.Uddin, 2019)

3. "Machine Learning-Based Gene Prioritization Identifies Novel Candidate Risk Genes for Inflammatory Bowel Disease" (Isakov, 2017)

Isakov et al. presented a supervised ML method to study the known genes to detect new genes connected to IBD. They studied transcriptomic data from existing data sets, and implemented XGBoost, elastic net regularized generalized linear model, RF, and SVM algorithms. The data sets were used for training (75%) and validation(25%). **They discovered 347 genes with high prediction scores for IBD and 67 new IBD risk genes** (no publication found relating them to IBD).

4. **CURATE.AI** – an AI-derived platform that uses a patient's prospectively/longitudinally acquired data to dynamically identify their own optimal and personalized doses, still under trial. (Blasiak, 2022)

4. Potential uses of AI for precision medicine include precision cardiology by analyzing various omics data (Sethi, 2023), various cancers (precision oncology), and many other diseases.

The examples also point to the fact that a lot of AI-supported Precision Medicine will be done through omics and other such data-intensive fields, but also through the integration of a patient's data over time (longitudinally) and across modalities. These are two different levels, yet they converge to the same endpoint – a customized treatment plan for the patient, supported by new omics findings, new drugs and dosage information, and new and better risk predictions and diagnosis techniques.

SUPPORTING ARGUMENTS

WHY WIDESPREAD AVAILABILITY OF PRECISION MEDICINE IS GOOD FOR THE HEALTH OF INDIVIDUALS AND COMMUNITY

1. Precise treatment of patients will lead to better risk prediction for diseases (which risk genes are present, which metabolites are disturbed, which drug will be more effective?), preventive interventions, and early diagnosis (risk genes present for colon cancer, diet is low in fiber? Get screening done and increase fiber intake), better clinical outcomes, fewer side effects. Of course, this is an ideal state and will take a long time to be achieved.

2. Population health – all the data from various precision medicine data sets will not only lead to many discoveries, from new risk genes and drug targets to environmental impacts on health, but they will also pave the way for prevention by identifying risk factors that can be contained or removed. Here are some ways precision medicine improves population health (CDC.gov)

a) Family health history can help you know which diseases you are more likely to get, then screening and preventive procedures can be started on time.
b) Personal devices can keep track of your health information. While this sounds great, the truth is integrating personal health device data into health tech is a long way from reality, and perhaps AI and the increased computational power can make this data transformation and integration happen.
c) Pharmacogenomics can help your doctor prescribe the drug and dose most likely to work for you. This is especially true for drugs that work by targeting genes or receptors, we saw an example earlier for a potential Alzheimer's drug Blaracmesine that had only one known target, but ML algorithms helped identify another one in AD patients.
d) Biomarker testing can help your doctor choose the best treatment. While common in Cancers, AI can help expand omics testing, for example - to metabolites (metabolomics) for chronic metabolic diseases, cardiovascular diseases, and even response to therapy in these conditions.

WHY AI IS CRUCIAL TO MAKING PRECISION MEDICINE A COMMON MEDICAL PRACTICE

Currently, Precision Medicine is used only for specific cases like cancers, and as explained in the introduction, the main deterrent is the inability to harness all the data available about a patient, and in the field of medicine, to practice precision medicine. This bottleneck, this resource limitation, this inability to process data from all modalities and create information, and use it timely, is solved by – AI.

Most arguments for AI in Precision Medicine have been made in literature discussions - AI allows integration of different modalities of data (images, EHR, genomic) and arrives at usable outcomes like stroke prediction or identification; AI enables usage of vast genomic data for diagnosis, treatment, and research; AI enables analysis of complex data to find new patterns and associations, etc. One topic not discussed earlier is cost saving.

How does AI in precision medicine lead to **cost savings**? Almost 90% of drugs do not pass the trial phase (Sun, 2022), and this 'wastage' is in billions, but AI and precision medicine, with methods like machine reading, data analysis, and predictive modelling, can help reduce these costs.

Another avenue where cost saving occurs is the actual practice of precision medicine that **reduces unnecessary treatments and procedures**. Example (CDC.gov) – A patient has Tourette syndrome, and is to be treated with 'Pimozide', a drug that is metabolized differently in some people. Genetic testing for the gene CYP2D6 shows a version of CYP2D6 that breaks down pimozide slowly. So, the doctor will now use a lower dose. This does two things **– increase patient safety by reducing side effects, and prevent unnecessary treatment with higher doses.**

CHALLENGES TO AI'S USE IN PRECISION MEDICINE

DATA SETS (EMERITUS.ORG, 2024; ALOWAIS, 2023)

1. Lack of good quality data sets for training AI models is a major challenge. The clinical data sets need to be well-distributed, large, and diverse, otherwise, the output from the models will be skewed and incorrect, and thus, not good enough to be used in clinical practice.

2. Data Set shifting – any model based on data from EHRs is susceptible to change in EHR model/ algorithm, and shifting patient population. (Kelly, 2019)

Mitigation – Data sets for training should be well chosen, and if new data is being collected for training, bias prevention by including a diverse population (age, race, gender, ethnicity) should be done.

‘AI CHASM’ – THE GAP BETWEEN PERFORMANCE METRICS AND CLINICAL RELEVANCE

AI performance metrics are usually measured by ‘Area Under Curve of ROC’ but this is not a good measure for healthcare models. This gap between a sound AI model vs its actual use in the real -world is called the **AI chasm** (Keane, 2018).

Mitigation - This can be reduced by using clinically relevant measures to define output like sensitivity, specificity, PPV, and NPV, and also educating the clinicians about how the AI model works, so they can understand the output better. (Kelly, 2019)

BIAS AND THEIR IMPACT ON HEALTH EQUITY FOR UNDERREPRESENTED MINORITIES (URM)

As AI is trained on existing research and data, the biases they carry for age, race, gender, and socio-economic background, are amplified in AI models. An example of this is the **AI detection of skin moles** for classification into benign or malignant. While the results were comparable to dermatologists, the model being trained on a poorly diverse data set was able to **identify lighter skin moles much more accurately**. (Guo, 2022; Ory, 2023; Kelly, 2019)

HALLUCINATIONS BY AI

AI can often produce incorrect output, and present it as ‘correct’ instead of ‘understanding’ that it does not have the actual answer. This problem remains true for AI in medicine also, an example being – **‘Watson for Oncology (WFO)**, which is an AI-powered decision support system for oncology. It **recommended incorrect treatments**, especially for countries outside the USA, and one of the reasons cited was that the training data sets had some ‘synthetic patient data’. (Jie, 2021; Bryant, 2018; Gerke, 2020)

Ideally, the system should understand that it cannot provide the correct output for the situation, but AI often doesn’t, leading to ethical and legal issues.

OTHER CHALLENGES TO AI IN PRECISION MEDICINE

These are more general points that are a challenge to AI use in healthcare, including Precision Medicine.

1. Data privacy and security issues – There is a lot of concern about how the collected patient data used for training AI models can be misused without the patient’s

consent. Transparency and informed consent in a way that patients understand where the data is going and how it will be used is important. (Gerke, 2020)
In the USA, ensuring HIPPA compliance while integrating AI is also an area that is not very well defined, and can lead to legal issues.

2. Human Barriers to AI adoption in healthcare – both patients' and providers' trust in AI is a barrier, and hopefully as policy and regulations become better, and technology more reliable, this will reduce.

3. Logistical Interoperability issues – A major issue currently, most different data sets in health tech are not interoperable with each other, or with other hospitals' EHR, given that interoperability hasn't been achieved in the existing health tech, the application of AI models to this technology has interoperability issues.
Mitigation -This can be improved by unified data formats, adopting FHIR, and developing standards for AI/ML with clinical systems.

4. Legal and Ethical risks – Privacy, security, data misuse, acting on incorrect recommendations, there are plenty of ethical and legal conundrums with a technology like AI.

FUTURE

In 2021, the AI in healthcare global market was 11 billion USD, **by 2030, it is projected to be 188 billion USD** (Statista.com). Some AI-supported Precision Medicine possibilities are –

1. **AI-integrated EHRs**, with complete **interoperability**, able to collect data, send it to data integration points, train and update AI models; able to convert unstructured data into AI/ ML standard processed data; able to include omics data, etc. (Denny, 2021)
2. **Longitudinal data collection** (over the patient's life, rather than episodic fragmented data we have today) about a patient, that could lead to profiling, usage of AI (Big Data) to identify actionable health points, and even perform predictive risk analysis. (Schüssler-Fiorenza Rose, 2019; Denny, 2021)
3. **Policy** and regulations that support AI and innovation, while securing patient's right to their data and its usage.

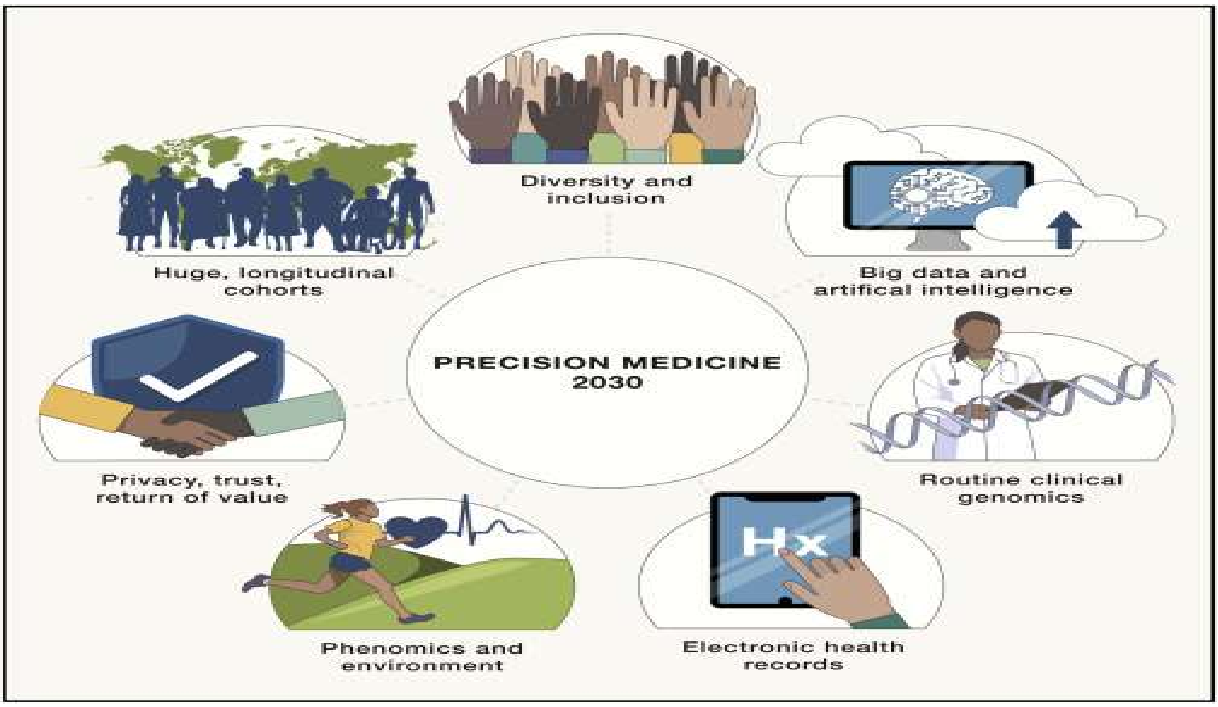

Figure 12. Precision Medicine - what to expect by 2030. (Denny, 2021)

CONCLUSION

In Conclusion, while limitations, concerns for patient safety, data safety, privacy, and logistic challenges remain, AI could truly UNLEASH the power of information from the vast amount of collected health data, to customize treatment for a patient, assess their risks to many diseases, and recommend best possible health interventions and preventions for the individual, rather than the current 'one size fits all' treatment.

In the USA, this is also encouraged by the fact that a lot of health data is already electronic, states are pushing incentives for technology and interoperability, and advanced techniques like DNA sequencing and biomarker assays are becoming faster and cheaper.

There is a long way to go, but as of now, it is only AI that can address this bottleneck of vast fragmented data, and its processing into useful information.

REFERENCES

1. Subramanian, M., Wojtusciszyn, A., Favre, L. et al (2020).. Precision medicine in the era of artificial intelligence: implications in chronic disease management. *J Transl Med 18, 472*. https://doi.org/10.1186/s12967-020-02658-5
2. Jørgensen, J. T. (2019). Twenty Years with Personalized Medicine: Past, Present, and Future of Individualized Pharmacotherapy. *The Oncologist, 24(7), e432–e440*. https://doi.org/10.1634/theoncologist.2019-0054
3. *What is precision medicine?:* MedlinePlus Genetics. (n.d.). https://medlineplus.gov/genetics/understanding/precisionmedicine/definition/
4. Ginsburg, G. S., & Phillips, K. A. (2018). Precision Medicine: From Science to Value. *Health Affairs, 37(5), 694–701*. https://doi.org/10.1377/hlthaff.2017.1624
5. *What is Artificial Intelligence (AI)?* | IBM. (n.d.). https://www.ibm.com/topics/artificial-intelligence
6. *Artificial intelligence in healthcare: defining the most common terms*. HealthITAnalytics. (2024, April 3). https://healthitanalytics.com/features/artificial-intelligence-in-healthcare-defining-the-most-common-terms
7. *Understanding the different types of artificial intelligence*. IBM Blog. (2023, October 16). https://www.ibm.com/blog/understanding-the-different-types-of-artificial-intelligence/
8. Sethi, Y., Patel, N., Kaka, N., Kaiwan, O., Kar, J., Moinuddin, A., Goel, A., Chopra, H., & Cavalu, S. (2023). Precision Medicine and the future of Cardiovascular Diseases: A Clinically Oriented Comprehensive Review. *Journal of Clinical Medicine, 12*(5). https://doi.org/10.3390/jcm12051799
9. Aronson, S., & Rehm, H. L. (2015). Building the foundation for genomics in precision medicine. *Nature, 526(7573), 336–342*. https://doi.org/10.1038/nature15816
10. Genomics-Enabled learning health care systems. (2015). In *National Academies Press eBooks*. https://doi.org/10.17226/21707
11. Kim, J., & Lee, B. (2018). Identification of Alzheimer's disease and mild cognitive impairment using multimodal sparse hierarchical extreme learning machine. *Human Brain Mapping, 39*(9), 3728-3741. https://doi.org/10.1002/hbm.24207
12. Kline, A., Wang, H., Li, Y., Dennis, S., Hutch, M., Xu, Z., Wang, F., Cheng, F., & Luo, Y. (2022). Multimodal machine learning in precision health: A scoping review. *Npj Digital Medicine,* 5(1), 1-14. https://doi.org/10.1038/s41746-022-00712-8
13. Zihni, Esra & Madai, Vince & Khalil, Ahmed & Galinovic, Ivana & Fiebach, Jochen & Kelleher, John & Frey, Dietmar & Livne, Michelle. (2020). Multimodal Fusion Strategies for Outcome Prediction in Stroke. 421-428. 10.5220/0008957304210428.
14. Cai, Z., Poulos, R. C., Liu, J., & Zhong, Q. (2022). Machine learning for multi-omics data integration in cancer. *iScience, 25*(2), 103798. https://doi.org/10.1016/j.isci.2022.103798
15. Vadapalli, S., Abdelhalim, H., Zeeshan, S., & Ahmed, Z. (2022). Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine. *Briefings in Bioinformatics, 23*(5). https://doi.org/10.1093/bib/bbac191
16. *Support Vector Machine (SVM) algorithm*. GeeksforGeeks. (2023, June 10). https://www.geeksforgeeks.org/support-vector-machine-algorithm/
17. *What is Random Forest?* | IBM. (n.d.). https://www.ibm.com/topics/random-forest#:~:text=Random%20forest%20is%20a%20commonly,both%20classification%20and%20regression%20problems.
18. *What is XGBoost?* (n.d.). NVIDIA Data Science Glossary. https://www.nvidia.com/en-us/glossary/xgboost/
19. *What is natural language processing?* | IBM. (n.d.). https://www.ibm.com/topics/natural-language-processing

20. NLP Summit. (2021, April 20). *Machine Reading for Precision Medicine - Healthcare NLP Summit.* https://www.nlpsummit.org/machine-reading-for-precision-medicine/
21. Lee, I., Celik, S., Logsdon, B. A., Lundberg, S. M., Martins, T. J., Oehler, V. G., Estey, E. H., Miller, C. P., Chien, S., Dai, J., Saxena, A., Blau, C. A., & Becker, P. S. (2018). A machine learning approach to integrate big data for precision medicine in acute myeloid leukemia. *Nature Communications*, 9. https://doi.org/10.1038/s41467-017-02465-5
22. Hampel, H., Williams, C., Etcheto, A., Goodsaid, F., Parmentier, F., Sallantin, J., Kaufmann, W. E., Missling, C. U., & Afshar, M. (2020). A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the Blarcamesine (ANAVEX2-73) Phase 2a clinical study. Alzheimer's & Dementia : *Translational Research & Clinical Interventions, 6*(1). https://doi.org/10.1002/trc2.12013
23. Uddin, M., & Wang, Y. (2019). Artificial intelligence for precision medicine in neurodevelopmental disorders. *Npj Digital Medicine, 2*(1), 1-10. https://doi.org/10.1038/s41746-019-0191-0
24. Isakov, O., Dotan, I., & Ben-Shachar, S. (2017). Machine Learning-Based Gene Prioritization Identifies Novel Candidate Risk Genes for Inflammatory Bowel Disease. *Inflammatory bowel diseases, 23*(9), 1516–1523. https://doi.org/10.1097/MIB.0000000000001222
25. Blasiak, A., Truong, A. T. L., Jeit, L. T. W., Kumar, K. S., Tan, S. B., Teo, C., Tan, B. K. J., Tadeo, X., Tan, H. L., Chee, C. E., Yong, W., Ho, D., & Sundar, R. (2022). PRECISE CURATE.AI: A prospective feasibility trial to dynamically modulate personalized chemotherapy dose with artificial intelligence*. Journal of Clinical Oncology, 40*(16_suppl), 1574. https://doi.org/10.1200/jco.2022.40.16_suppl.1574
26. *Precision health: Improving health for each of us and all of us* | CDC. (n.d.). https://www.cdc.gov/genomics/about/precision_med.htm
27. Sun, D., Gao, W., Hu, H., & Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it? *Acta Pharmaceutica Sinica. B, 12*(7), 3049-3062. https://doi.org/10.1016/j.apsb.2022.02.002
28. Kelkar, G. (2024, February 28). *Top challenges of AI in healthcare: What businesses need to resolve*. Emeritus Online Courses. https://emeritus.org/blog/healthcare-challenges-of-ai-in-healthcare/
29. Alowais, S. A., Alghamdi, S. S., Alsuhebany, N., Alqahtani, T., Alshaya, A., Almohareb, S. N., Aldairem, A., Alrashed, M., Saleh, K. B., Badreldin, H. A., Yami, M. S. A., Harbi, S. A., & Albekairy, A. (2023). Revolutionizing healthcare: the role of artificial intelligence in clinical practice. *BMC Medical Education, 23*(1). https://doi.org/10.1186/s12909-023-04698-z
30. Keane, P. A., & Topol, E. J. (2018). With an eye to AI and autonomous diagnosis. *Npj Digital Medicine, 1*(1), 1-3. https://doi.org/10.1038/s41746-018-0048-y
31. Guo, L., Lee, M. S., Kassamali, B., Mita, C., & Nambudiri, V. E. (2022). Bias in, bias out: Underreporting and underrepresentation of diverse skin types in machine learning research for skin cancer detection—A scoping review. *Journal of the American Academy of Dermatology, 87*(1), 157–159. https://doi.org/10.1016/j.jaad.2021.06.884
32. Ory, M. G., Adepoju, O. E., Ramos, K. S., Silva, P. S., & Dahlke, D. V. (2023). Health equity innovation in precision medicine: Current challenges and future directions. *Frontiers in Public Health, 11.* https://doi.org/10.3389/fpubh.2023.1119736
33. Jie, Z., Zhiying, Z., & Li, L. (2021). A meta-analysis of Watson for Oncology in clinical application. Scientific Reports, 11(1), 1-13. https://doi.org/10.1038/s41598-021-84973-5
34. Bryant, M. (2018, July 26). *STAT: IBM's Watson gave 'unsafe and incorrect' cancer treatment advice.* Healthcare Dive. https://www.healthcaredive.com/news/stat-ibms-watson-gave-unsafe-and-incorrect-cancer-treatment-advice/528666/
35. Gerke, S., Minssen, T., & Cohen, G. (2020). Ethical and legal challenges of artificial intelligence-driven healthcare. *Artificial Intelligence in Healthcare, 295-336*. https://doi.org/10.1016/B978-0-12-818438-7.00012-5

36. *Topic: AI in healthcare*. (2024, January 10). Statista. https://www.statista.com/topics/10011/ai-in-healthcare/#topicOverview
37. Denny, J. C., & Collins, F. S. (2021). Precision medicine in 2030—Seven ways to transform healthcare. *Cell, 184*(6), 1415-1419. https://doi.org/10.1016/j.cell.2021.01.015
38. Schüssler-Fiorenza Rose, S. M., Contrepois, K., Moneghetti, K. J., Zhou, W., Mishra, T., Mataraso, S., Dagan-Rosenfeld, O., Ganz, A. B., Dunn, J., Hornburg, D., Rego, S., Perelman, D., Ahadi, S., Sailani, M. R., Zhou, Y., Leopold, S. R., Chen, J., Ashland, M., Christle, J. W., . . . Snyder, M. P. (2019). A Longitudinal Big Data Approach for Precision Health. *Nature Medicine, 25*(5), 792. https://doi.org/10.1038/s41591-019-0414-6