Is It Time for the A-I (Allergist-Immunologist) to Embrace AI (Artificial Intelligence) in DX and RX of the Inborn Errors of Immunity (IEIs)?

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Objectives

Upon completion of this learning activity, participants should be able to:

- Understand how artificial intelligence (AI) is transforming DX and RX of IEIs
- Identify key applications of AI in DX and RX strategies for IEIs.
- Describe how AI can enhance diagnostic precision, improve treatment efficacy, and optimize patient outcomes in IEIs

Lecture Outline

- Introduction
- What is Artificial Intelligence (AI)?
- Phenotypes, Endotypes, and Genotypes in IEIs
- Applications/Challenges of AI in DX and RX of the IEIs
- Ways the A-I Can Use AI in DX and RX of the IEIs
- Practical Examples of AI in the DX and RX of IEIs
- Conclusions

Introduction

- Dr. William B. Schwartz, in a prescient article published in the NEJM in 1970 (1), envisioned a future where computers would serve as a powerful extension of the physician's intellect, revolutionizing medical practice.

- In a second NEJM article (2), by Dr. Schwartz, published 17 years later, he reaffirmed his foresight, acknowledging the formidable challenges in developing truly reliable AI-driven programs but maintaining his unwavering conviction that AI would one day transform the DX and RX of disease.

- Now, more than fifty years after his initial vision, the extraordinary rise of AI in medicine stands as a testament to the brilliance and prophetic clarity of Schwartz's predictions.

1. Schwartz WB. Medicine and the computer. The promise and problems of change. N Engl J Med. 1970; 283:1257-64.
2. Schwartz WB, Patil RS, Szolovits P. Artificial intelligence in medicine. Where do we stand? N Engl J Med. 1987; 316:685-8.

INTRODUCTION

- The IEIs are >500 genetic disorders of the immune system, most commonly associated with increased susceptibility to infections
- It is increasingly recognized that AI has evolved from a theoretical concept into an essential tool in modern healthcare.
- A review of the recent literature highlights AI's potential to enhance precision medicine in allergy-immunology, particularly in diagnosing and managing Inborn Errors of Immunity (IEIs)
- The aim this presentation is to explore the evolving role of AI in the DX and RX of IEIs, highlighting its potential to advance precision medicine for the allergist-immunologist.

Tangye SG, et al. J Clin Immunol. 2022; 42:1473-1507.

What is Artificial Intelligence (AI)?

- AI refers to algorithms that mimic human cognitive functions like reasoning and decision-making.

- Machine Learning (ML): A subset of AI that improves with data input, divided into:
  - Supervised Learning – Learns from labeled datasets.
  - Unsupervised Learning – Identifies patterns in unstructured data.

- AI's ability to process large datasets makes it valuable in healthcare applications.

Phenotypes, Endotypes, and Genotypes in Inborn Errors of Immunity (IEIs)

Characteristic	Definition	Example
Phenotype	An observable distinguishing feature of a disease, such as a morphologic, developmental, biochemical, or physiologic property, or behavior, without any implication of a mechanism.	Physical appearance of the patient, e.g., short stature, low-set ears in Di George syndrome; recurrent; warts in WHIM syndrome.
Endotype	A distinct functional or pathobiologic mechanism(s) that brings about the immune deficiency condition, e.g., history of recurrent infection, history of autoimmunity or autoinflammatory disease.	Abnormal oxidative metabolism in Chronic Granulomatous Disease (CGD).
Genotype	A genotype refers to the genetic constitution or genetic makeup of the affected host that will identify definitive genetic etiologic markers of the various forms of the inborn errors of immunity (IEIs)	Deficient Bruton Tyrosine Kinase (BTK) activity in X-linked Agammaglobulinemia (XLA).

Artificial Intelligence – Applications and Challenges in DX and RX of the IEIs?

DX IEI

- AI can analyze complex clinical PHENOTYPIC. ENDOTYPIC and GENOMIC data for early DX and personalized RX of the IEIs.

- AI-driven algorithms readily improves obtaining PHENOTYPIC. ENDOTYPIC and GENOMIC data and risk prediction, and disease identification of the IEIs.

- Challenges include:
  - Limited datasets for rare IEIs.
  - Integration with Electronic Health Records (EHRs).
  - Algorithmic bias and data privacy concerns.

- Ethical considerations must be addressed for fair and accurate implementation.

Practical Examples of AI in the DX and RX of IEIs

- Six sample of IEIs were created that the A-I is called upon to diagnose (DX) and treat (RX)

- Each case using a clinical vignette that includes a brief history (HX) and pertinent laboratory findings.

- The IEIs consisted of 5 of the more commonly seen IEIs consisting the following:

  1) Severe Combined Immunodeficiency (SCID);
  2) Common Variable Immunodeficiency (CVID);
  3) Chronic Granulomatous Disease (CGD);
  4) X-Linked Agammaglobulinemia (XLA):
  5) Wiskott-Aldrich Syndrome (WAS);

  and a sixth recently described IEI,

  6) Activated PI3K Delta Syndrome (APDS).

Practical Examples of AI in the DX of IEIs

Vignette 1 SCID	Vignette 2 CVID	Vignette 3 CGD	Vignette 4 XLA	Vignette 5 WAS	Vignette 6 APDS
J.D., a 6-mos-old ♂, with recurrent infections since birth, pneumonia, OM, oral thrush, and chronic diarrhea. (FTT), Is malnourished, PXs generalized wasting,, iritability, and pallor. Absent thymic shadow on X-ray.	J.S is a 28-yr-old ♀ with a 5 yr HX of recurrent respiratory infections, pneumonia, sinusitis, bronchitis, fatigue and chronic diarrhea. PX reveals a tired, thin ♀ T 36.9°C HEENT: Clear cardiac normal; abdomen: soft,, no organomegaly;	M.B. is a 12-yr-old ♂ with multiple recurrent skin infections, persistent lymphadenitis, and recurrent pneumonia. He has also developed granulomatous lesions on his skin and in his GI tract. PX multiple healed scars from previous infections, several active granulomatous lesions on the forearms.	A 9-mos-old ♂ with recurrent bacterial infections starting at 6 mos, multiple OM, sinusitis, chronic diarrhea, G&D normal PX small, infant in mild respiratory Ht,Wt < 10th %. HEENT: Bilateral ear discharge, crackles in lower lung fields	E.D. is a 3-year-old male with a HX of recurrent infections, eczema, and prolonged bleeding and OM. A maternal uncle had a history of easy bruisability. PX 3-year-old male with pa llor Ht,Wt < 10th %.	G.R. is a 10-yr-old male with recurrent URI, and chronic diarrhea with FTT. Over the past year, has developed persistent lymphadenopathy and hepatosplenomegaly PX bilateral large 3-4 cm cervical lymph nodes, hepatomegaly> 4cm,
Lab findings Lymphopenia (ALC 800/μL) Markedly reduced T,B and NK cells.	**Lab Findings** Normal WBC with slight lymphopenia. • IgG: 450 mg/dL • IgA: 30 mg/dL • IgM: 20 mg/dL	**Lab findings** Elevated WBC, mild anemia, normal IG levels, NBT negative, DHR test abnormal, liver abscess, Staphylococcus aureus from skin lesion.	**Lab findings** Elevated WBC IgG, IgA, IgM levels Undetectable, absent CD19+ B cells Genetic testing revealed the diagnosis.	**Lab findings** Hb= 11.0 g/dL; WBC 4,500/μl; platelet 21,000/μL decreased IgM; elevated IgA and IgE; poor Ab response to vaccine.	**Lab findings** Lymphocytosis, mild anemia; Low IgG, normal IgA and IgM. Increased transitional B cells, activated T cells. Enlarged liver & spleen.

Six clinical vignettes of the following IEIs were created which the allergist-immunologist may be called upon to DX and RX each with a brief clinical HX and pertinent laboratory findings.

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

A 9-mos-old male FTND HX of recurrent bacterial infections starting at 6 months of age. Multiple Severe OM, sinusitis, and requiring hospitalization and IV antibiotics. Chronic diarrhea for past 2 months. Growth and development normal until the recurrent infections began. No known family history of immunodeficiency disorders. PX reveals a small, underdeveloped infant in mild respiratory distress Temp 38°C, heart rate 90/min, respiratory rate 30/min, BP 90/60. Height and weight < 10th %. HEENT: Bilateral ear discharge, erythematous tympanic membranes. Lymphatic System: Absence of palpable lymph nodes. Respiratory: Crackles in the right lower lobe with decreased breath sounds. Gastrointestinal System: Mild abdominal distension, hyperactive bowel sounds. . Laboratory tests: CBC: elevated total WBC count, 12,000 mm3 with 80% neutrophils and 10% band forms. Immunoglobulin Levels:

- IgG: Undetectable
- IgA: Undetectable
- IgM: Undetectable

Flow Cytometry: Absence of CD19+ B cells in Genetic testing was performed which revealed the diagnosis.

Each clinical vignette was entered into ChatGPT with the prompt:

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

What is the most likely IEI that the vignette represents?

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

XLA

Following the correct diagnosis, a second query was introduced was entered into ChatGPT with the prompt:

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

XLA

Which is the mutation that may have led to this condition?

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

GENOTYPIC Description
BTK deficiency

Following the correct diagnosis, a third query was entered into ChatGPT with the prompt:

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

XLA

What is the most appropriate treatment for XLA?

a. SCID)
b. CVID)
c. CGD)
d. XLA)
e. WAS
f. APDS)

PHENOTYPIC Description

Lifelong IVIG or SCIG replacement, infection management

AI-Assisted Diagnostic Correlation with its Corresponding Phenotypic Clinical Vignette Description

- Each of the other phenotypic descriptions of the clinical vignettes was entered into ChatGPT with the prompt *'What is the most likely IEI that the vignette represents?* and ChatGPT consistently identified the correct diagnosis from the given list, demonstrating its potential as a diagnostic aid.

Clinical Vignette	AI-Assisted Diagnosis
SCID	SCID
CVID	CVID
CGD	CGD
XLA	XLA
WAS	WAS
APDS	APDS

AI-Assisted Genetic Correlation with its Corresponding Phenotypic Clinical Vignette Description

- Following the correct diagnosis, a second query was posted for each of the other IEIs to assess AI's diagnostic utility, with the prompt *'What is the mutation that may have led to this condition?'* ChatGPT was able to accurately associate each condition with its corresponding genetic mutation.

Clinical Vignette	AI-Assisted Diagnosis	Genetic Mutation
SCID	SCID	Mutation in the X-linked gene IL2RG
CVID	CVID	TNFRSF13B (TACI) mutation
CGD	CGD	Gp91phox deficiency
XLA	XLA	BTK deficiency
WAS	WAS	WAS gene mutation
APDS	APDS	PIK3CD gene mutation

AI-Assisted Treatment Recommendations

- Following the correct AI-assisted diagnosis, a third query was posted for each of the other IEIs to assess AI's therapeutic utility, with the prompt *'What is the most appropriate treatment for each of the six IEIs? '* ChatGPT correctly identified the standard treatment approaches for each disorder, reinforcing its potential as a clinical decision support tool

Clinical Vignette	AI-Assisted Diagnosis	AI-Assisted Treatment Recommendations
SCID	SCID	Hematopoietic stem cell transplantation (HSCT), gene therapy, IVIG or SCIG replacement
CVID	CVID	Immunoglobulin replacement, antibiotics for infection control
CGD	CGD	Antimicrobial PX, interferon-ɣ RX, HSCT in severe cases
XLA	XLA	Lifelong IVIG or SCIG replacement, infection management
WAS	WAS	HSCT, IG replacement, splenectomy in select cases
APDS	APDS	PI3K inhibitors [e.g., leniolisib (Joenja)], immunoglobulin replacement, immunosuppressants

SUMMARY of AI-Assisted Diagnosis, AI-Assisted Genetic Correlation and AI-Assisted Treatment Recommendations

- Each of the phenotypic descriptions of the 6 clinical vignettes was entered into ChatGPT with the prompt *'What is the most likely IEI that the vignette represents?* and ChatGPT consistently identified the correct diagnosis from the given list, demonstrating its potential as a diagnostic aid.

- Following the correct diagnosis, a second query was posted for each of the other IEIs to assess AI's diagnostic utility, with the prompt *'What is the mutation that may have led to this condition?'* ChatGPT was able to accurately associate each condition with its corresponding genetic mutation.

- To further assess AI's usefulness, a third query was posted for each of the other IEIs to assess AI's therapeutic utility with the prompt, *What is the most appropriate treatment for each of the six IEIs?* ChatGPT correctly identified the standard treatment approaches for each disorder, reinforcing its potential as a clinical decision support tool

Conclusions

- It has been said that AI won't replace physicians, but physicians who use AI will replace physicians who do not.
- As we navigate the evolving landscape of allergy-immunology and IEI, this quote serves as a powerful reminder: embracing AI as a tool for enhancing clinical decision-making is not about replacing the physician's expertise but about augmenting it.
- The future belongs to those who integrate AI into their practice to provide more precise, efficient, and personalized patient care.
- There will be challenges ahead in adopting AI for the A-I in the DX and RX of IEIs—but with thoughtful implementation, collaboration, and continued learning, we can look forward to a future where AI empowers us to care for our patients better than ever before.