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PRECISION MEDICINE IN DERMATOLOGY

Dermatology

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KEYWORDS

Precision medicine, Stratified medicine

INTRODUCTION

The practice of medicine has evolved over centuries from those based on empirical knowledge to currently practiced evidence-based approach. Evidence-based medicine (EBM) is an interdisciplinary approach which uses techniques from science, engineering, biostatistics and epidemiology, such as meta-analysis, risk-benefit analysis and randomized controlled trials to deliver treatment.

While some individuals may benefit considerably more than the average population included in the study, others might benefit significantly less, while no benefit or even significant harm may occur in some individuals. On the contrary "precision medicine" refers to tailoring of medical treatment to specific characteristics of each patient, classifying individuals into subpopulations that are uniquely susceptible to a specific treatment, sparing expense and side effects. [1]

What is Precision Medicine?

According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." It is in contrast to 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.[2]

Although the term "precision medicine" is relatively new, the concept has been a part of healthcare for many years. For example, during blood transfusion, donor's blood type is matched to recipient to reduce the risk of complications.

Precision Medicine Initiative:

The Precision Medicine Initiative is a long-term research endeavor, involving the National Institutes of Health, USA and multiple other research centers, launched in 2015 which aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease.

The short-term goals involve expanding precision medicine in the area of cancer research. The long-term goals focus on bringing precision medicine to all areas of healthcare on a large scale. All of Us Research Program, launched by NIH, involves a cohort of at least 1 million volunteers (both healthy and diseased) from around US who are providing genetic data, biological samples, and other information about their health. Researchers can use these data to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies.[2]

Some related terms:

Personalized medicine: National Research Council describes "personalized medicine" as an older term with a meaning similar to "precision medicine." Due to concern that the word "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual; the Council therefore preferred "precision medicine".[2]

Stratified medicine: It includes identifying subgroups of patients with distinct mechanisms of disease or with specific responses to treatments and develop treatments that are effective for particular subgroups. This involves treating patients based on genetic profile, molecular basis of their disease, risk of disease and response to a particular drug therapy, rather than signs or symptoms of their disease.

The term 'stratified medicine' is considered more accurate as it reflects the realistic effects of treatment at subpopulation level, while the term 'personalized medicine' reflects possibly overambitious promise of individualized unique drug targeting and development.[3]

Precision medicine focuses on stratification of patients using large-scale data including clinical, lifestyle, genetic and biomarker information, thus going beyond the classical "signs-and-symptoms" approach. For example, in atopic dermatitis (AD):

1. **Stratification based on genotype:** Filaggrin loss-of-function mutations are the most common genetic susceptibility to AD but are found in only 10% to 40% of patients. These patients are characterized by reduced barrier function, increased allergic sensitization and contact allergy, higher severity, protracted course, and frequent skin infections.[4]
2. **Stratification based on phenotype:**

- Based on age of onset into infantile AD, childhood onset AD, adolescent onset AD, adult onset AD and AD in elderly. Majority of those with infantile onset AD go into complete remission before 2 years of age; those with childhood onset tend to have chronic disease and those with older age of onset tend to have very severe disease and high IgE levels.
- Based on severity into mild, moderate and severe. This stratification is helpful in deciding the treatment as well as comparing the efficacy of different therapies from various studies.

3. **Stratification based on endophenotype:**

Endophenotypes are a subset of biomarkers along the pathway between clinical phenotype and genotype that enables us to stratify highly complex diseases into subgroups for which more tailored prevention and therapeutic strategies have to be developed.

- Screening biomarkers allowing identification of patients with high risk of AD before first clinical signs of the disease - Transepidermal water loss, TSLP, TARC/CCL17.
- Severity biomarkers are used for evaluation of therapeutic response in the context of long-term disease control. CCL17, CCL22, CCL27, IL-31, IL-33, IL-22, IL-16 are used for biomarker-based stratification and predicting the possible benefit of therapeutic and prevention approaches.
- Predictive biomarkers for therapeutic response and/or risk of side effects for a given drug- It is hypothesized that AD in childhood shows a TH2, TH9, and TH17 polarization and in adults more TH22 dominant suggesting that current biologics targeting TH2 cytokines would be even more effective in children than in adults.[4]

Deep phenotyping is defined as the precise and comprehensive analysis of phenotypic abnormalities and classification of patients into subgroups based on distinct phenotype. It gathers details about disease manifestations and provide more specificity and potential connections between disease subtypes and genetic variations.

Big Data refers to omics' data produced by new-generation sequencing or genomics (entire genome), proteomics (peptide abundance, modification, and interaction), epigenome (reversible modifications of DNA or DNA-associated proteins, such as DNA methylation or histone acetylation), transcriptome (post transcription RNA levels),

metabolomics (multiple small molecule types, such as amino acids, fatty acids), foodomics (nutritional constituents), immunomics (proteomics and integrated serology), lipidomics (lipid metabolism), microbiomics (microorganisms colonizing humans).

Multiomics is a new approach where the data sets of different 'omic' groups like genome, proteome, transcriptome, epigenome , and microbiome are combined during analysis. These data can be useful both as markers of the disease process and to give insight as to which biological pathways or processes are different between the disease and control groups.[5]

Machine learning is an artificial intelligence technique that focuses on designing machines (or computers) that mimic human pattern recognition and problem solving and provides algorithms which are able to learn automatically and improve from experience without being explicitly programmed. Machine learning in precision medicine involves the development of novel algorithms for analyses of large well-curated datasets (Big data) and providing clinically relevant implications as discussed below.

Applications of precision medicine:

1. Prediction of adverse drug reactions
2. Prediction of responses to therapy in oncologic dermatology, autoimmune and rheumatologic skin disease.
3. To identify associations between comorbidities and risk factors
4. To study the genetic basis of diseases by using next-generation sequencing.
5. To recognize disease prognosis
6. Provides promising generalized framework that leverages gene expression data and "multi-omics" for biomarker discovery in autoimmune skin diseases, and for biologics and immunotherapies.

Examples of Precision medicine

1. **Earlier diagnosis and intervention:** Studies have shown that among women who inherit the BRCA1 mutation, 55–65% will develop breast cancer by the age of 70 years. Forty-five percent of women who inherit the BRCA2 mutation will develop breast cancer by 70 years of age, as compared with 12% of women in the general population. A noninvasive method of cancer prevention like regular screening or tamoxifen as antiestrogen therapy has shown to be beneficial among women with BRCA2 mutations specifically and reduced breast cancer risk by 62%.[6]
2. **Optimal treatment selection:** Trastuzumab has been shown to be effective in breast cancer patients with positive Her2 status and improved overall survival in late-stage (metastatic) HER2-positive breast cancer from 20.3 to 25.1 months.[7]
3. **Predicting Disease Prognosis:** In HIV patients on antiretroviral therapy, the risk of a new AIDS event or death follows a CD4 cell count gradient. It is an indicator of immune function and disease progression and one of the key determinants for the need of opportunistic infection prophylaxis.
4. **More efficient medicine development:** Cystic fibrosis is a multisystem disease caused by loss or dysfunction of the CFTR protein. Improved understanding of CFTR protein dysfunction has allowed the development of mutation-specific, small-molecule compounds called Ivacaftor which targets G551D mutation in CFTR gene, who account for 4–5% cases of cystic fibrosis.[8]
5. **Predicting drug adverse effects:** Penicillin skin prick testing has well defined negative predictive values with some reports showing 97%, indicating that patients with a history of penicillin allergy and negative skin test have a 3% risk of reaction when challenged with penicillin.[9]

Even though applications in oncology have led the way for stratified medicine, and near-term stratified medicine development and implementation efforts continue to focus on cancer; there are growing number of non-cancer stratified medicine applications including infection, respiratory, cardiovascular, familial genetics, renal, neurology, diabetes, transplantation and rheumatology.

ROLE OF PRECISION MEDICINE IN DERMATOLOGY

The basis of pharmacogenomics is the hope that by identifying biomarkers as genetic variants, clinicians will be able to identify patients at high risk for developing severe drug hypersensitivities, interpret and individualize drug therapy. Application of precision medicine in predicting adverse events and its role psoriasis have been tabulated in Table I and Table II.

Table I: Precision Medicine In Predicting Drug Adverse Events

Genetic mutation	High risk population	Adverse event
HLA-B*15:02	Han Chinese patients in Vietnam, Cambodia, Reunion Islands, Thailand, India, Malaysia and Hong Kong	Carbamazepine-induced SJS
HLA-A*3101	Northern Europeans, Han Chinese and Japanese	Carbamazepine induced hypersensitivity syndrome
HLA-B*13:01	Chinese, Japanese, Indians, and Southeast Asians	Dapsone hypersensitivity syndrome
HLA-B*57:01		Abacavir hypersensitivity syndrome
HLA5801	European, Japanese, Thai	Allopurinol induced SCAR
G6PD deficiency	Southern Europe, the Mediterranean, the Middle East, and India	Dapsone-induced hemolytic anemia
TPMT deficiency	African-Caribbean origin	Azathioprine induced bone marrow suppression

Table Ii- Application Of Precision Medicine In Psoriasis

Psoriasis	Genetic mutation	Clinical features
Disease predisposition	IL36RN	• High risk of Generalized pustular psoriasis • More severe manifestation, earlier age of onset • Lesser prevalence of Psoriasis vulgaris
	HLA-Cw6	Distinguishing marker for psoriasis type I (early onset < 40 years) and type II (late-onset ≥ 40 years
Disease phenotype, course and prognosis:	HLA-Cw06	• Early onset of skin psoriasis • Late arthritis • Extensive cutaneous lesions • Positive family history for psoriasis • Greater prevalence of guttate phenotype
	HLA-B27	• High risk of PsA • Early onset of arthritis • Spondylitis (spinal joint, sacroiliac joint) • Distal interphalangeal joint arthritis • Uveitis • Male predominance • Poor prognosis
Treatment response	High BMI	• Poor response
	HLA-Cw06	• Better improvement to Methotrexate • Increased response to ustekinumab and efalizumab
	HLA-Cw06 negative	• More likely respond to adalimumab

ATOPIC DERMATITIS

Filaggrin mutations:

- Associated with AD associated asthma, allergic rhinitis.
- Early onset and persistent eczema.
- Sensitisation to grass, house dust, mites, and cat dander.

Serum IgE: Classifies AD into- extrinsic and intrinsic subgroups.

- Extrinsic AD (80%): Characterized by high total and

environmental serum IgE levels, eosinophilia, personal and family atopic background, and greater rate of filaggrin mutation.
- Intrinsic AD (20%): Characterized by normal IgE levels, female predominance, delayed disease onset, preserved barrier function, increased metal contact hypersensitivity.

Endotype based therapeutic approach:
Based on various endotypes expressed by AD patients, they are subdivided to offer specific therapeutic measures to each subgroup.
- TH2 endotype – dupilumab - IL-4 receptor mAb that blocks IL-4 and IL-13.
- TH17 endotype- Secukinumab - anti–IL-17 targets IL-17/IL-23 pathway.[9]

CHRONIC URTICARIA:

Disease prognosis:
1. **Clinical course:** Disease duration of more than 1 year and presence of angioedema are associated with worse prognosis.
2. **Predisposing factors:** Urticaria exacerbated by NSAID use are associated with worse prognosis.
3. **Biomarkers:** High levels of IL-6, IL-6sR, IL-18, MMP-9, CRP, D-dimer, CD 203c- basophils are associated with worse prognosis. Low levels of Vitamin D and basophil count are also associated with worse prognosis. [10]

Prediction of treatment response:

I. Predictors of response to antihistamines:
1. **CRP:** According to recent studies, high levels of CRP may predict poor response to antihistamines and good response to oral CsA.
2. **D-dimer:** Elevated D-dimer levels are often associated with refractory disease and poor response to antihistamine treatment.
3. **Platelet activating factor (PAF):** A higher UAS7 score and a PAF level ≥ 5000 pg/ml are significant predictors of a poor response to H1RA treatment.
4. **Complement 5 a receptor (C5AR1) single nucleotide polymorphism:** In a Chinese study, poorest response to desloratadine was observed in patients with heterozygous C5AR1 SNP −1330T alleles, when compared with homozygotes. Hence this is a useful pharmacodynamic predictor of nonsedating H1-antihistamines efficacy in CSU patients.[11]

II. Predictors of response to Omalizumab:
Serum IgE: High disease activity, presence of angioedema and lower IgE levels (<43 IU/ml) at baseline are common predictors of non-responders and faster relapse after discontinuing omalizumab.[12]
D- dimer: Elevated levels of D-dimer before treatment are associated with better response to omalizumab.

EPIDERMOLYSIS BULLOSA:

In current clinical practice, management of EB is mainly supportive but identification of mutant genes has provided the basis for development of novel molecular therapies which are currently at preclinical level. An example of precision medicine currently being developed for treatment of EB, is read-through of premature termination codon mutations, which are common in autosomal recessive forms of EB. Patients with recessive dystrophic epidermolysis bullosa (RDEB) have nonsense mutations in the gene encoding type VII collagen leading to premature stop codons that result in truncated collagen. Aminoglycoside induced collagen has been shown to reverse the abnormal RDEB cell phenotype. Hence aminoglycosides (geneticin, gentamicin, and paromomycin) may have therapeutic potential for RDEB patients with mutations leading to premature stop codons.[13]

CONCLUSION

Precision medicine includes stratification of patients based on clinical, lifestyle, genetic and biomarker information, thus going beyond the classical "signs-and-symptoms" approach. It enables tailoring effective treatment and prevention strategies for specific subgroup of patients. In current clinical practice, applications of precision medicine in dermatology are very limited and further research is required to increase its scope and provide holistic, individually tailored therapy.

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