Biomarkers and personalized medicines in paediatrics

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The event is part of the European Biotech Week 2020

Paediatric drug research

Exclusion of children from clinical trials prior to 1970.

In 1977, the American Academy of Pediatrics Committee stressed that it was critical to conduct appropriate drug studies in children

Paediatric drug research is still lagging behind adults.

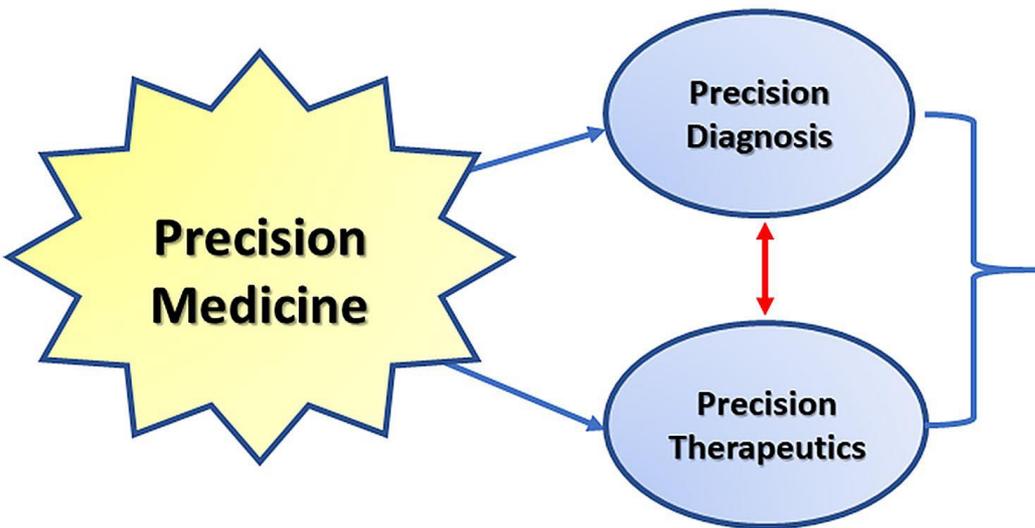Major areas of need:

Developmental disease characterisation

Developmental pharmacodynamics,

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Precision/Personalised medicine

- 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." the Precision Medicine Initiative,

- "The provision of the right treatment to the right patient at the right dose at the right time". the Pharmaceutical Committee of European Commission

- Stratified medicine: Selection of the best approach to managing a group of patients.

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Requirements for precision medicine

Precision Medicine → Precision Diagnosis ↔ Precision Therapeutics

| Biomarker Types	Purpose
Susceptibility/Risk Biomarker	Indicates the potential for developing a disease or medical condition or sensitivity to an exposure in an individual without clinically apparent disease or medical condition
Diagnostic biomarker	Identify individuals with the disease or condition of interest or to define a subset of the disease
Monitoring biomarker	Measured serially and used to detect a change in the degree or extent of disease; may also be used to indicate toxicity or assess safety, or to provide evidence of exposure, including exposures to medical products
Prognostic biomarker	Used to identify likelihood of a clinical event, disease recurrence or progression.
Predictive biomarker	Used to identify individuals who are more likely than similar patients without the biomarker to experience a favorable or unfavorable effect from a specific intervention or exposure
Pharmacodynamic/Response biomarker	Used to show that a biological response has occurred in an individual who has received an intervention or exposure.
Safety Biomarker	Used to indicate the presence or extent of toxicity related to an intervention or exposure
Surrogate Endpoint	Used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives; does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence

Pediatric Clinical Endpoint and Pharmacodynamic Biomarkers: Limitations and opportunities
https://doi.org/10.1007/s40272-019-00375-1

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Biomarkers

The Food and Drug Administration (FDA) National Institutes of Health Biomarker Working Group defines a biomarker as a **"defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions."**
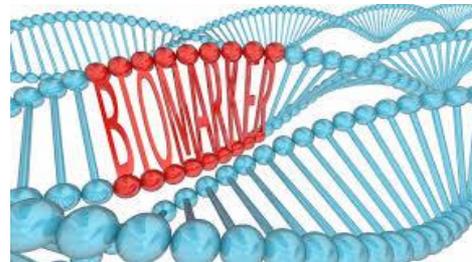
Precision Diagnosis for children

Hampered by inadequate disease characterisation

Interpreted through established adult disease symptoms

e.g. Juvenile vs adult onset rheumatoid arthritis

- more heterogenious pathology

- limited disease overlap

- adult biomarkers mostly uniformative

Paediatric-specific biomarkers are clinically important for accurate diagnosis and overall paediatric care

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Precision Therapeutics for children

- Developmental effects on pharmacodymanics and pharmacokinetics are crucial.

- Potentially highly variable (especially early in life)

- Resulting in potentially different ideal drug concentrations compared to adults

Paediatric asthma

Asthma is a heterogeneous and multifactorial respiratory disease

Characterised by

- airway inflammation,

- airway hyper-responsiveness (AHR),

- and reversible airway obstruction.

Affects around 15% of school-aged children in Europe.

Symptoms

- wheezing,

- shortness of breath,

- chest tightness,

- cough,

ranging in severity from mild symptoms to life-threatening exacerbations

Managing paediatric asthma

International guidelines established for drug treatment

Reliever medication

- Short-acting beta-agonists (SABAs)

- rapid-onset bronchodilation mediated by the activation of adrenergic receptors

Controller medication

- inhaled corticosteroids (ICSs),

- anti-inflammatory and immunosuppressive lung tissue

- interact with the glucocorticoid receptor

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Managing paediatric asthma

Controller medication (more severe asthma)

- long-acting beta-agonists (LABAs)

- Leukotriene receptor antagonists (LTRAs)

Severe asthma

- oral corticosteroids (OCSs),

- systemic effects

- incidence of adverse reactions increases with OCS treatment

- application limited to the most severe cases

Personalized medicine in asthma management

Based on identifying different asthma phenotypes and **endotypes** ('subtypes of a condition defined by a distinctive functional or pathophysiologic mechanism)

Asthma endotypes

- type 2 (T2)-high asthma
- type 2 (T2)-low asthma

T2 high asthma

Characterised by eosinophilic inflammation

- Trigger in bronchial epithelium

- ''Alarmin'' (e.g. IL-25 and IL-33) secretion

- Release of Type 2 cytokines (IL-4, IL-5, and IL-13)

- Recruitment of eosinophils/ mast cells/basophils

- Synthesis of IgE

Good response to corticosteroid therapy

Target of biological therapies

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T2 low asthma

Neutrophilic or granulocyte-poor inflammation

- IL8, IL-17A, IL-22 involevement

- Rare endotype

- Mainly in severe patients

- Corticosteroid insensitivity

Current Biomarkers in Childhood Asthma

Biomarker	Sample type	Associated asthma endotype	Proposed use
Eosinophil	Serum, sputum	T2-high	Disease phenotyping Severity of clinical symptoms Monitoring of asthma control Prediction of treatment response
Neutrophil	Sputum	T2-high/T2-low	Disease phenotyping Under investigation
IgE	Serum	T2-high	Disease phenotyping Severity of clinical symptoms
Periostin	Serum	T2-high	Disease phenotyping Severity of clinical symptoms Diagnosis Prediction of treatment response
FeNO	Exhaled air	T2-high	Disease phenotyping Severity of clinical symptoms Monitoring of asthma control
IL-17	Serum	T2-low	Disease phenotyping
EBC	Exhaled air	Not yet determined	Under investigation
VOCs	Exhaled air	Not yet determined	Under investigation

EBC, exhaled breath condensate; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; T2, type 2; VOCs, volatile organic compounds

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Summary of biologics approved for pediatric asthma

Biologic	Mechanism of Action	FDA Approval Age	Indications	Predictors of Response
Omalizumab	Humanized, monoclonal anti-IgE binding free IgE	≥6 y old	Moderate-to-severe persistent asthma, symptoms inadequately controlled with ICS, perennial aeroallergen sensitization	Elevated $F_E NO$ Elevated serum eosinophils Body mass index of ≥25 Exacerbations on NHLBI 5 therapy
Mepolizumab	Humanized, monoclonal antibody binding to IL-5	≥12 y old	Severe persistent asthma, eosinophilic phenotype	Elevated serum eosinophils Frequent exacerbations
Benralizumab	Humanized, monoclonal ab against the IL-5a receptor leading to ab-dependent cell-mediated cytotoxicity	≥12 y old	Severe persistent asthma eosinophilic phenotype	Elevated serum eosinophils Frequent exacerbations
Dupilumab	Fully humanized, monoclonal antibody against the IL-4 a receptor blocking both the IL-4 and IL-13 pathways	≥12 y old	Moderate-to-severe persistent asthma, eosinophilic phenotype, or with oral corticosteroid dependent asthma	Elevated serum eosinophils Frequent exacerbations Elevated $F_E NO$

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Useful publications

- Pediatric Clinical Endpoint and Pharmacodynamic Biomarkers: Limitations and opportunities. **doi.org/10.1007/s40272-019-00375-1**

- Asthma Endotyping and Biomarkers in Childhood Asthma. **doi.org/10.1089/ped.2018.0886**

- It's Time to Start Phenotyping Our Patients with Asthma. **doi.org/10.1016/j.iac.2019.07.009**

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