**Drug development in children benefits from OMICs:**

**a c4c expert group white paper**

***Revised version***

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# **Abstract**

The safety and efficacy of pharmacotherapy in children, particularly preterms, neonates, and infants, is limited by a paucity of good quality data from prospective clinical drug trials. A specific challenge is the establishment of valid biomarkers. OMICs technologies may support these efforts, by complementary information about targeted and non-targeted molecules through systematic characterization and quantitation of biological samples. OMICs technologies comprise at least genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics in addition to the patient’s phenotype. OMICs technologies are in part hypothesis-generating allowing an in depth understanding of disease pathophysiology and pharmacological mechanisms. Application of OMICs technologies in paediatrics faces major challenges before routine adoption. First, developmental processes need to be considered, including a sub-division into specific age groups as developmental changes clearly impact OMICs data. Second, compared to the adult population, the number of patients is limited as well as type and amount of necessary biomaterial, especially in neonates and preterms. Thus, advanced trial designs and biostatistical methods, non-invasive biomarkers, innovative biobanking concepts including data and samples from healthy children, as well as analytical approaches (e.g. liquid biopsies) should be addressed to overcome these obstacles. The ultimate goal is to link OMICs technologies with innovative analysis tools, like artificial intelligence at an early stage. The use of OMICs data based on a feasible approach will contribute to identify complex phenotypes and subpopulations of patients to improve development of medicines for children with potential economic advantages.

# **I****ntroduction**

The interindividual variability in efficacy and safety of drugs in both adults and children complicates the selection of the right drug and the right dose for the individual patient. The extrinsic and intrinsic factors that contribute to interindividual variability include disease status, organ function (e.g. liver, kidney), age, weight and lifestyle as well as drug adherence (Lonergan et al. 2017; Zanger und Schwab 2013). Around 20% of adverse drug reactions (ADRs) are dose independent which cannot be explained from a drug’s conventional pharmacology. Those ‘off-target’ drug effects may be explained by other factors, including pharmacogenomics (PGx) variation (Abdullah-Koolmees et al. 2021; Osanlou et al. 2018).

With the improved knowledge of the human genome, genetic variation has been identified as a crucial

influencing factor on pharmacotherapy and disease. Thus, PGx research is widely accepted in the drug develoment process including clinical trial activities. Of note, a significant number of drug labels already include PGx information for the adult population (Food and Drug Administration 2020) and international consortia like the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network (Réseau) of Pharmacogenetics (RNPGx) provide substantial guideline information (Abdullah-Koolmees et al. 2021). In the meantime, it is well accepted that drug safety and efficacy in children can also benefit substantially from PGx research. In addition, developmental aspects that modify drug targets and ADME (**A**bsorption, **D**istribution, **M**etabolism, **E**limination) processes must be considered as well. This includes changes in the body composition and organ function, the expression and function of drug metabolizing enzymes and transporters as well as pharmacodynamics drug targets such as receptors and specific proteins (e.g. guanine nucleotide-binding proteins) (Kearns Gregory L. et al. 2003). Thus a more comprehensive approach is warranted and in the meantime an initiative has been started to collect information on paediatric ontogeny by a well-organized knowledge base (Burckart et al. 2020). Comprehensive translational and clinical research activities are needed to gather robust data during the drug development process in the paediatric population. This review aims to address specifically various approaches, commonly termed as OMICS technologies (Table 1) which should be considered more instensively early in the development process for medicines in children and clinical trial initiatives.

This review reflects a collaboration between researchers from the Innovative Medicines Initiative conect4children (IMI c4c) Expert group on Pharmacogenomics and other OMICS technologies (IMI).

**Genomics and P****harmacogenomics (PGx)**

Genetic testing for variants underlying inherited diseases is a fundamental part of the health system since decades. Regarding inherited genetic diseases childhood is the crucial period for testing to prevent negative long-term effects. Several diagnostic procedures are well established and implemented in clinical practice early after birth or even during pregnancy (e.g. screening for trisomy 21). To achieve nationwide testing for a number of severe inherited diseases that are amenable to therapeutic strategies (e.g. phenylketonuria), high-income developed countries and a steadily growing number of low- and middle-income countries have established the newborn screening programmes (NBS) to detect inborn errors of metabolism early after birth to provide subsequent therapeutic strategies. Diagnostic methods include classical laboratory tests like immunoassays, functional assays such as the detection of endogenous compounds via mass-spectrometry, but also - more increasingly - genomic procedures such as next generation sequencing. Genetic testing of the *CFTR*-Gene for early detection of cystic fibrosis is, for example, part of the NBS besides the screening of non-genetic parameters (e.g. immunoreactive trypsinogen). CFTR modulators like ivacaftor and lumacaftor are labelled for treatment of children carrying variants which result in a gating defect (CFTR class III variants) and/or a CFTR folding defect (e.g. F508del). Most recently, a conferred additional benefit regarding efficacy and safety in children ≥ 12 years of age carrying the Phe508del-gating or Phe508del-residual function variants has been reported for the CFTR modulator regimen using elexacaftor, tezacaftor and ivacaftor compared to previous CFTR modulators (Barry et al. 2021). This example highlights the concept of PGx in children and the study of variations of germline DNA related to drug response (Carter und McKone 2016).

However, consideration of PGx in the drug development process in children remains limited compared to the adult setting, where use of genomics to define disease susceptibility, prognosis and improvement of drug response is more broadly implemented (Green 2019). Until December 2020 the FDA listed 431 pharmacogenomic biomarkers in drug labeling of which about 40% were related to oncology (Food and Drug Administration 2020). A total of 165 clinical annotation guidelines and 784 drug label annotations are currently available at the PharmGKB website (PharmGKB). Moreover genetic variation supports not only better prediction of efficacy and/or safety of pharmacotherapy but also helps to identify new targets.

Numerous publications arising in the last decade have emphasized the importance of paediatric PGx (Gregornik et al. 2021; Stevens et al. 2013; Hawcutt et al. 2013; Elzagallaai et al. 2021; Maagdenberg et al. 2016). As in adults, oncology is also pioneering in paediatric PGx and the example of treatment of childhood acute lymphoblastic leukemia demonstrates this enormous progress (Franca et al. 2020). Here, the risk of toxic events in response to drug treatment can be significantly reduced by the consideration of PGx information on thiopurine haematoxicity and *TPMT* and *NUDT15* genotypes (Relling et al. 2019; Schaeffeler et al. 2019) and on vincristine-related neurotoxicity and variants in the gene encoding the centrosomal protein CEP72 (Diouf et al. 2015; Wright et al. 2019).

Evidence for the benefit of preemptive and/or point-of-care PGx testing is growing (Krebs und Milani 2019). The challenge for the implementation process of PGx into clinical practice is currently well addressed by various expert groups worldwide (Chenoweth et al. 2020; Sing et al. 2015; Brown et al. 2019; Brown et al. 2021) but requires evidence-based data from clinical trials. As mentioned above, information by the CPIC, the DPWG, the CPNDS and RNPGx includes evidence-based PGx recommendations for dose-adjusted treatment or alternative drug therapy according to pheno-/ genotypes. Paediatric recommendations are part of PGx guidelines, but data are mostly limited based on the small number of studies involving children (Aka et al. 2017; Ramsey et al. 2020). An overview of the currently published CPIC Guidelines and specific pediatric recommendations is given in Table 2. PGx guidelines with relatively robust paediatric data are also available for non-cancer drugs like e.g. atomoxetine and CYP2D6 (Brown et al. 2019) as well as tacrolimus and CYP3A5 (Birdwell et al. 2015). The increased risk of aminoglycoside-induced hearing loss in association with variants of the *MT-RNR1* gene is another well-accepted example (McDermott et al. 2021) since in young children hearing skills are not fully developed and the impact of ototoxicity is particularly high. Regarding the different PGx guidelines (i.e. CPIC, DPWG, CPNDS, RNPGx) some discordances exist, although the committees have similar methodologies of gudieline development (Abdullah-Koolmees et al. 2021). For instance, cisplatin-induced hearing loss has been associated with an increased risk particularly in children carrying TPMT variants (Drögemöller et al. 2019) and the FDA added PGx information to the cisplatin drug label (Food and Drug Administration 2020). However, so far only the CPNS strongly recommends TPMT genotyping in children prior to starting a therapy with cisplatin (Lee et al. 2016).

The increasing acceptance of paediatricans to implement PGx guidelines is corroborated by a recent survey of paediatric providers in the United States and Japan indicating that in > 80% PGx was considered to improve paediatric drug efficacy and/or safety (Rahawi et al. 2020). Moreover, a very recent retrospective analysis indicates that there is a high prevalence of diagnoses and actionable gene-drug-diagnostic groups in children and adolescents. Almost half of tested patients (220 of 452, 48.7%) had a clinical diagnosis where their PGx testing could influence treatment and 15.0% received a medication where the PGx test result could be used for dose adjustment (Roberts et al. 2021).

With advancing diagnostic technologies PGx testing becomes faster and cheaper and more attractive in clinical practice as well as for drug development. Beyond hypothesis generating research whole genome and exome sequencing including short read next generation sequencing are increasingly implemented into clinical routine and used for gene diagnostics of diseases as well as for PGx profiling (Caspar et al. 2021). Targeted approaches like oligonucleotide microarrays or mass spectrometry based assays (MALDI-TOF) to detect known SNPs and CNVs are also very well established. GWAS can yield not only disease susceptibility genes, but also clinically relevant PGx information, as was nicely shown in the example of childhood leukemia (Franca et al. 2020). One of the first landmark papers regarding GWAS PGx demonstrated that flucloxacillin-induced liver injury is associated with the *HLA-B\*5701* allele (Daly et al. 2009). Other GWAS examples with relevance for children followed such as the association of immediate penicillin hypersensitivity with HLA-DRB1\*10:01 providing insights into the mechanisms of immediate reactions (Nicoletti et al. 2021), and the higher incidence of hypersensitivity (p=7.5 x105, odds ratio 1.64) and anti-asparaginase antibodies (p=1.4x105, odds ratio 2.92) in children with asparaginase treatment for leukemia/lymphoma and HLA-DRB1\*07:01 (Fernandez et al. 2014).

In this context GWAS have proven useful to inform drug repurposing and to identify causal relationships between druggable exposures and complex disorders. For instance thousands of variants which have been identified through GWAS related to clinically relevant phenotypes contribute to better understanding of genes and pathways involved in disease pathophysiology. Mapping of genome-wide significant loci to drug targets with consequences for currently used or repurposed compounds is Is highly promising for pediatric drug development und innovative medicines in children (Reay WR, Cairns MJ. Advancing the use of genome-wide association studies for drug repurposing. Nat Rev Genet. 2021).

What is widely accepted for inherited diseases, that early diagnosis and therapy yields the best prognosis, holds also true for PGx. The earlier the PGx status of a child is known the better the pharmacotherapy can be tailored to the individual patient avoiding acute as well as negative long-term effects due to inappropriate pharmacotherapy (Adam de Beaumais und Jacqz-Aigrain 2018), which also holds true for the drug development process. This is especially important for the vulnerable paediatric patient groups where side effects or lack of drug efficacy may result in lifelong damage. Moreover, the impact of developmental aspects on enzyme activity, metabolic pathways and other ADME processes is mandatory to consider as well, particularly in the first years of life. Notably, this dynamic maturation process of protein expression and function has the potential to alter the phenotype which is first identified from the genetic information (van den Anker et al. 2018). Thus, the correlation between genotype and phenotype may still differ from adults since for instance posttranscriptional processes are also subject to developmental alterations and crucial for protein function. This means that a poor metabolizer phenotype may be determined by the quantitation of plasma levels of a specific drug, although genetically the patient is a heterozygous carrier of a functional relevant PGx variant. This phenomenon is well known in a figurative way in adult medicine and termed as phenocopying. Here heterozygous patients result in a poor metabolizer phenotype due to inhibition of the remaining enzyme activity via drug-drug interaction (Shah und Smith 2015). Taken together, convincing examples are given that PGx research in paediatrics will promote individualized treatment and therefore PGx concepts should be strongly followed in clinical trial activities during the drug development process (Johnson et al. 2019).

# **E****pigenomics**

Whereas the genome remains constant in an individual across their lifetime, the epigenome is highly flexible, dynamic and responsive. Epigenetic modifications play an important role in gene expression and silencing, including DNA methylation (which is the most investigated), histone modification and miRNA expression (Berdasco und Esteller 2019). Extensive DNA methylation plasticity is known to occur during embryogenesis. This is crucial for development and maintenance of cellular differentiation and identity. The fact that monozygotic twins exhibit similar epigenomes early in life, which diverge increasingly with increasing age, demonstrates the impact and the responsive nature of epigenetics (Mario F. Fraga et al 2005). In oncology specific epigenetic profiles are associated with cancer development, thereby demonstrating the relationship between the epigenome and disease (Ortiz-Barahona V. et al. 2020). Given the fact that the epigenome is highly responsive to the environment, these findings can shed light on the mechanism behind disease acquisition due to external risk factors. Reprogramming during pregnancy as a consequence of epigenomic modulation may result in specific paediatric phenotypes even after birth (Felix et al. 2018; Placek et al. 2019), nicely shown by the example of the Prader-Willi syndrome and transient neonatal diabetes mellitus (Mendiola und LaSalle 2021).

Alongside the contribution from genomics, investigation of epigenomics is proposed to contribute to our understanding of the interindividual variability of drug response including ADRs, and also to promote the development of new epigenetic drugs (Fisel et al. 2016). With regard to childhood cancer, not only the spectrum of cancer types and their incidence differ from adults, but also genetic- and epigenetic profiles. Although generally paediatric cancers contain fewer mutations, interestingly a higher frequency of genetic variants encoding for epigenetic regulators has been found for cancer types such as brain tumors, neuroblastoma, and retinoblastoma (Yiu und Li 2015).

The impact of ageing in adults on DNA methylation is well-addressed with consequences on drug targeting and treatment strategies (Bell et al. 2019). Different studies and meta-analyses comparing paediatric and adult data demonstrate qualitative and quantitative differences in DNA methylation patterns occurring over lifetime. Moreover, there is increasing evidence that epigenetic regulation via DNA methylation has a major impact on the expression of pharmacogenes (e.g. ADME genes) which promotes research activities termed as pharmacoepigenomics (Fisel et al. 2016). It has been shown that DNA methylation of transcription factor binding sites within the *CYP3A* promoter in mice and humans explain the switch from CYP3A7 expression in embryonic livers to CYP3A4 in postnatal tissues (Kacevska et al. 2012). Comparable results were found for CYP2W1 expression indicating silencing of expression of CYP2W1 by epigenetic regulation in healthy adult tissues compared to fetal gut (Guo et al. 2016). Regarding drug transport, hyper- and hypomethylation of efflux - and uptake transporter proteins from the ABC- (e.g. ABCB1, ABCG2) and SLC-transporter families (e.g. OCT1, MCTs) are well-described with consequences for pharmacokinetics and pharmacodynamics (Fisel et al. 2016; Fisel et al. 2018; Neul et al. 2016).

To this end, pharmacoepigenomics needs to be adressed more systematically in paediatric drug research. Of note, epigenetic analyses are tissue specific and this may limits the feasibility of research activites in children where the availability of tissue biopsies is extremly limited. However, the noninvasive approach of DNA methylation analysis in body fluids like blood using cell-free circulating DNA warrant futher investigations.

# **T****ranscriptomics**

In addition to DNA sequencing and epigentic studies, transcriptomics adds the information on gene expression, thereby taking the next step towards the elucidation of mechanisms describing discrepancies between geno- and phenotypes. Of note epigenomic alterations of the RNA itself are well-known (Liang et al. 2020; Zhao et al. 2017) as are feedback mechanisms of transcriptomic products on the epigenome (Zhang et al. 2020). Similar to epigenomics, transcriptome analyses are cell/tissue specific (Wang et al. 2008).

In general posttranscriptional modifications are fundamental for the functionality of the cytochrome P450 superfamily enzymes, which are essential for the metabolism of xenobiotics (Annalora et al. 2017). Types of posttranscriptional modifications include the processing of pre-RNAs through alternative splicing, capping or polyadenylation into functional mature RNA; and alternative splicing is an important site of functional influence for genetic polymorphisms in drug-metabolizing enzymes, transporters and other drug targets, as nicely shown for by the *CYP3A5\*1* variant (Sadee et al. 2011). Interestingly, alternative splicing may be age-dependent and explain part of the developmental change in ADME protein expression, as recently shown for the hepatic uptake transporter SLCO1B1 (van Groen et al. 2020).

The majority of trait-associated SNPs are not located in protein coding regions, and are likely to act via modification of gene expression. eQTL studies (i.e. expression quantitative trait loci) are going beyond univariate SNP-transcript associations and differentiate in cis- (i.e. located within the transcribed gene region) and trans- (i.e. distant) eQTLs to uncover biological pathways, polygenetic effects of expression regulation, including for instance the enrichment of co-localized functional elements. Several eQTL-studies in different adult tissues (e.g. human liver) have been published (Schröder et al. 2013), however with the limitation on small sample sizes. Novel technologies to cover more diverse, disease-relevant cell types have been recently suggested (Umans et al. 2021). Whilst hybridization-based microarrays for transcriptional profiling have been used to provide information on diagnosis, prognosis and optimal treatment (Meyer et al. 2013), current approaches combine RNA-Seq with advanced bioinformatic approaches to interrogate large datasets including the many possibly relevant transcript variants.

Many paediatric diseases can be classified by their transcriptomic response, and transcriptomic approaches have also improved our understanding of the pathology of paediatric diseases as well as of therapeutic interventions, thereby contributing significantly to drug development. Beyond paediatric cancer (Rusch et al. 2018; Shiba et al. 2019), transcriptomic profiles of diseased tissue offer a window into a wide range of paediatric conditions including inflammatory bowel disease (Howell et al. 2018), and juvenile idiopathic arthritis (Kessler et al. 2018). RNA-Seq approaches can complement genomic sequencing to yield improved genetic diagnoses in Mendelian disease with consequences for drug therapy and drug development (Cummings et al. 2017). Whole blood represents a convenient body compartment for sampling, and whole blood studies have identified diagnostic signatures that support diagnosis in otherwise difficult-to-diagnose conditions (Gliddon et al. 2018). In infectious diseases, blood signatures may be pathogen-specific (Herberg et al. 2013), or class-specific (Herberg et al. 2016), and enables understanding of disease progression, for instance in tuberculosis (Mulenga et al. 2020). The utility of transcriptomics for biological understanding and diagnosis extends beyond infectious problems to inflammatory conditions such as Kawasaki Disease (Wright et al. 2018), and non-inflammatory conditions including neonatal encephalopathy (Montaldo et al. 2019). Finally, there is evidence that a transcriptome-wide association approach is able to identify functionally-relevant genetic associations which has been recently shown for severe anthracycline-induced cardiotoxicity and the association with the growth/differentiation factor 5 (Scott et al. 2021). We therefore encourage paediatric clinical trials to incorporate sampling for transcriptomic studies particularly in combination with other analyses such as genomic approaches.

**P****roteomics**

Epigenomics and transcriptomics are crucial for better understanding of phenotype-genotype correlations. In addition, protein data provides definite information on the expression of target proteins. This information is most important, as mRNA levels may not correlate with protein expression. Several molecular and biochemical reasons for such discrepancies are well known such as the variety of transcripts, the regulation via miRNAs, proteasomal degradation and posttranslational modifications. Proteomics covers exhaustive analytical methods including mass-spectrometry tecniques such LC-MS/MS and MALDI-TOF/TOF (Aslam et al. 2017). An additional challenge is the identification of proteins for hypothesis-generating research which requires huge libraries and advanced IT systems. Protein biomarkers in adults are used for diagnosis, monitoring of disease progression and/or treatment response dictations as part of the drug development process (Dupree et al. 2020). A specific area in drug research is pharmacoproteomics with examples such as carboplatin and paclitaxel resistance in ovarian cancer (Cruz et al. 2017). Promising results of a combination of pharmacoproteomics with PGx have been reported for warfarin (Saminathan et al. 2010) and recently DrugBank (DrugBank), a web-enabled database, has been updated which contains comprehensive information about drugs and related issues such as targets and interactions. Of note the new version DrugBank 5.0. provides additional highly interesting data on pharmacoproteomics (Wishart et al. 2018).

Paediatric proteomic research has also been widely conducted in some areas including acute lymphablastic leukemia (López Villar et al. 2014), type 1 diabetes (Ioanna Kosteria et al. 2018) and ventilator-induced lung injury (Pereira-Fantini et al. 2018). Regarding developmental aspects and medicines in children, proteome analyses showed remarkable differences reflecting again the impact of developmental regulation in tissues as well as specific cell types (Froehlich et al. 2014). Although a huge number of potentially relevant protein biomarkers is identified each yea in drug research, only a small number reach validation and approval by the FDA (Füzéry et al 2013). Although a diverse variety of database is available, the major limiation is still a more powerful bioinformatics support for database searching. More innovative interdisciplinary approaches considering the combination of various OMICs approaches should be addressed early in the drug development process.

# **M****etabolomics**

In addition to proteomics, metabolomics allows for the identification of metabolic profiles through qualitative and quantitative data on a multitude of small-molecules. For metabolomics analyses various biofluid samples including serum, plasma, urine and cerebrospinal fluid as well as tissue samples (e.g. biopsies), and exhaled breath can be used. Beyond the identification of specific biomarkers for disease susceptibility and drug response, bioinformatics-driven complex pathway analyses based on metabolomics are promising. In recent years, it has been recognized that the metabolic pattern reflects the functional status of an individual more comprehensively than other approaches such as genomics, as metabolic profiles incorporate the influence of additional factors including diet, environmentent, or the gut microbiome (Pang et al. 2019). Here, again developmental aspects resulting in functional consequences particularly related to paediatric medicines are included (Beger et al. 2016). As mentioned above, the Guthrie test, which has been routinely used for decades, is an excellent example of a metabolomic screening test for inborn errors (here elevated concentration of phenylalanine and galactose in blood) is based on metabolomics (Mordaunt et al. 2020). Novel mass-spectrometry technologies improved NBS significantly measuring a huge variety of endogenous compounds in a less time- and cost-consuming manner (Bessey et al. 2020). Moreover innovations like next-generation metabolic screening as an untargeted metabolomics approach appear to be promising (Coene et al. 2018). Beyond NBS metabolomics is well established for diagnosis of other diseases in childhood. One major advantage is that non-invasive biosamples can be used, such as urine (Hanna und Brophy 2015), saliva, and blood. Methodologies like dried blood spots are being introduced to overcome the limited amount of biomaterial particularly in the preterm- and newborn setting.

Untargeted assays allow large-scale and hypothesis-generating approaches in paediatric research to identify and characterize novel compounds which significantly expand our knowledge not only related to disease pathophysiology (e.g. childhood asthma (Turi et al. 2018) or infection (Wang et al. 2019) but also related to drug-related metabolic alteration (Trivedi et al. 2017; Ellul et al. 2019). Another promising non-invasive method in paediatric metabolomics is breathomics with specific focus on exhaled volatile organic compounds (VOC) in paediatric asthma (Neerincx et al. 2017). VOCs in exhaled breath come from the lungs, but also via the lungs from the general circulation, and various techniques (e.g. electronic nose analysis, mass spectrometry) and be used for analysis. Notably breathomics allows the detection of bacterial and/or viral infections (Lammers et al. 2021), the amount of inflammatory cells in blood (Vries et al. 2018), different diagnosis of respiratory diseases (Moor et al. 2021) and response to medication (Vries et al. 2019).

The application of metabolomics and better understanding of endogenous metabolism in nutrition of neonates has been nicely shown by the work of Dessi et al (Dessì et al. 2014). A further interesting paediatric example is the application of metabolomics to differentiate between children with and without typical symptoms of gastro-intestinal disorders. Researchers were able to show that an integrated profiling approach using metabolomics from urine and serum and cytokines is able to stratify successfully between children with appendicitis- and non-appendicitis-related abdominal pain, and perforated and non-perforated appendicitis (Shommu et al. 2018).

Thus, clinical trial monitoring not only involves monitoring of drug effects, but also diet, food by-products, additional drug use or abuse, herbal supplements, metabolism phenotypes in individual patients, etc. Implementation of pharmacometabolomics and particularly pharmacometabolomics-informed PGx in drug devlopment is increasing. Several excellent reviews (Neavin et al. 2016; Everett 2019; Beger et al. 2020) summmarize examples demonstrating that metabolomic profiles are associated with variable pharmacological response followed by the identification of sub-phenotypes based on better understanding of biochemical pathways and the pivotal role of individual variation in drug response phenotypes. Comprehensive collection of biomaterials such as blood and urine and consideration of metabolomic approaches in prediatric clinical trials will strengthen the drug development process in total.

# **M****icrobiomics**

The move to recognize the microbiome as a human organ has helped increase awareness of the microbiomic research in the scientific community (Baquero und Nombela 2012). Historically microbiome research was predominantely linked to microbial ecology, the study of the interaction of bacteria with their environment, and the effect on the ecosystems (e.g. plants and animal species). However, there is now convincing data demonstrating the microbiome’s impact on various diseases, such as gastrointestinal (e.g. inflammatory bowel diseases (Kostic et al. 2014; Nishida et al. 2018), or necrotizing enterocolitis (Sim et al. 2015) and hepatic diseases (e.g. hepatic steatosis (Nishida et al. 2018), several types of cancer (Fessler et al. 2019), asthma (Abdel-Aziz et al. 2019) as well as mental illnesses like major depressive disorder (Peirce und Alviña 2019). A strong interaction of the microbiome with the immune-, endocrine-, metabolic- and nervous system is well accepted (Gilbert et al. 2018). Thus, e.g. microbes colonize not only the gut but are also detected in the respiratory and genitourinary tract and tissues without disease-causing effects (Silbergeld 2017).

The microbiome underlies developmental processes as well, which requires age-specific research activites. Moreover, the impact of drug treatment on the microbiome with clinical consequence in later in life has nicely been shown for Caesarean section and early antibiotic exposure interfering with the natural microbiome development and obesity risk (Dominguez-Bello et al. 2019). Other examples are reported such as the association with progress for respiratory diseases (Man et al. 2017; Cuthbertson et al. 2020) and most strikingly the contribution of the microbiome in autism spectrum disorder (Hughes et al. 2018).

The concept of the therapeutic potential of the microbiome is emerging. Here, first evidence is reported in children with inflammatory bowel diseases (Nusbaum et al. 2018) and autism spectrum disorders (Kang et al. 2019) and the use of probiotics as well as the microbiota transfer. Very recently, Park et al. showed that the microbiome is in part responsible for the variability in the pattern of symptoms of chronic rhinosinusitis comparing data from adult and paediatric patients (Park et al. 2020). The gut microbiome may also have an impact on the first-pass metabolism of drugs. This has been shown for more than 50 drugs being metabolized by the gut microbiome, including drugs, which are used in daily practice like omeprazole (Haiser und Turnbaugh 2013). Moreover, the absorption (e.g. digoxin), the distribution (e.g. sulfasalazine) and the elimination (e.g. irinotecan) of drugs (Tuteja und Ferguson 2019) is also influenced by the microbiome. Here, future concepts include the topic of potential activation of selected prodrugs, depending on microbial metabolism, as demonstrated for azo drugs (phenazopyridine) used in inflammatory bowel disease therapy since decades (Wilson und Nicholson 2017). A very recent key paper strongly supports the impact of microbiomics and drug development. Here the authors provide evidence that the bioaccumulation of drugs by gut bacteria contribute significantly to drug avialablity and bacterial metabolism with consequences for pharmacokinetics, ADR and drug response (Klünemann et al. 2021). Thus, the microbiome is probably the most innovative OMICs field with enormous potential also for children and future therapeutic options.

# **C****onsequences for paediatric clinical trials**

Based on data from adults there is increasing evidence that various Omics technologies contribute substantially for better understanding of drug-related events which include efficacy as well as safety.

Regulators like the FDA accept biomarker information in the submission package for New Molecular Entities (NME) or Biologic License Application (BLA), and adaptive drug development concepts change traditional clinical drug development via phase 1 to 3 (Gromova et al. 2020).

Between 2015 and 2019 more than half of the EU and the US approvals were supported by biomarker data during at least 1 of the development stages (Gromova et al. 2020). Notably, the ICH Guideline E16 describing the context, structure, and format of qualification submissions for clinical and nonclinical genomic biomarkers related to drug development (ICH Expert Working Group) is applicable also to other types of biomarkers, thereby increasing the acceptance of biomarkers in the global drug development process (Amur et al. 2015).

There are challenges for the incorporation of Omics technologies in paediatric pharmacological research studies. Paediatric studies often include small numbers of participants in each age group; and there are ethical concerns concerning the obtaining of consent from both parents and child for the conservation and re-use of biosamples after their initial use in a study. There is substantial progress with regard to innovative analytical and computational technologies as well as novel study designs alongside biobanking initiatives in paediatric research. For example, urine and saliva as non-invasive specimen for proteomics and metabolomics analyses are feasible to obtain. Besides serum, saliva can be used for molecular analyses. Residual [material](https://www.dict.cc/?s=material) from routine clinical blood sampling in the context of pediatric drug trials as well as dried blood spots are alternatives. Very recently Forno and Celedón (Forno und Celedón 2019)reported that non-invasive access to nasal epithelial cells is useful to perform epigenomic analyses in childhodd asthma, since these cells are closely related to bronchial epithelial cells. However keeping in mind that some OMICs technologies are tissue specific such as DNA-methylation further concepts are neccesary to guarantee minimal burden according to ethical requirements (van Paemel et al. 2020). Moreover, Estrella et al. successfully used NBS blood spots for further analysis investigating biomarkers for disease pathophysiology of diabetes type 1 (Estrella et al. 2020). Pediatric drug trial protocols should consider from the beginning various OMICs technologies based on standardized and well-documented standard operation procedures including handling of biological samples in combination of precise phenotypic data for comprehensive data analysis and futher research activities.

Innovative IT-based modeling tools like physiologically-based pharmacokinetic (PBPK) modeling and system medicine approaches are crucial for an innovative future pediatric drug development process. PBPK enables the integration of various OMICs data based on information from drug trials and/or literature review including ontogenetic information to predict dosing of pediatric medicines, particularly in critical subpopulations like neonates. The concept of PBPK starts to build a specific PBPK model including subsequently evaluation based on adult data. Next, the model is scaled to the paediatric population for a priori prediction of pharmacokinetics and here, data from pediatric clinical trials is integrated comprising drug levels, physiological parameters, data on enzyme and/or transporter expression with consideration of developmental age-related alteration (Allegaert et al. 2017; Kovar et al. 2020; Verscheijden et al. 2020). Importanly PGx information for instance with impact on drug-related ADME processes can be included as well (Wojtyniak et al. 2021). A digitizing software solution as tool for PBPK modeling to gather data from graphical representations with excellent accuracy and precision has also been established (Wojtyniak et al. 2020). Novel concepts of a more holistic view based on multi-layer network theory and artificial intelligence may ensure better integration of multi OMICs data., as well (Fröhlich et al. 2018).

To this end, disease diagnosis, stratification, susceptibility, prognosis of disease and treatment response will substantially benefit from comprehensive consideration of multi-Omics approaches in paediatric research and clinical trial activities (Figure 1). Moreover comprehensive collection of various Omics data during the clinical phase of pediatric drug development will contribute to improve and even optimze the subsequent drug development process which has been nicely outlined for adult clinical trials and their impact on R&D productivity (Paul et al. 2010).

Beyond well-defined and “systematic” biobanking and omics strategies within trials, the systematic assessement of paediatric phenotypic data, the use of electronic health records and/or other digital applications as well as innovative IT-based analysis tools are most challenging. To obtain a better understanding of gene-environment interactions, as well as potential treatment options, a holistic approach is needed that combines non-genetic factors and multi-OMICs driven information with modeling and simulation to predict drug response profiles which are exploited to generate evidence-based treatment decisions.

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**Legend to the Figures.**

**Figure 1.**

Information flow and application of OMICS technologies to personalized medicine in children. The integration of clinical data and data from genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics based prior biological knowledge enables the opportunity to develop specific classifiers for personalized medicine.

A central element of this workflow is the systematic computational network analysis comprising various approaches.

 **Table 1. Summary of OMICs technologie**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **OMICs methods** | **Biomaterial** | **Methodology** | **Information** | **Application** | **Examples** |
| **Genomics** | DNA germline and/or somatic | targeted (e.g. gene panel) and untargeted (e.g GWAS, NGS) methods | Individual genetic make-up | Identification and usage of known or new genetic biomarkers for diagnosis and treatment decisions | Abdullah-Koolmees et al. 2021Barry et al. 2021 Caspar et al. 2021McDermott et al. 2021Nicoletti et al. 2021Franca et al. 2020Brown et al. 2019Drögemöller et al. 2019Relling et al. 2019Schaeffeler et al. 2019Wright et al. 2019Carter & McKone 2016Lee JW et al. 2016Birdwell et al. 2015Diouf et al. 2015Fernandez *et al.* 2014 Daly et al. 2009 |
| **Epigenomics** | DNA/RNA, protein (tissue specific) | Targeted and untargeted (e.g. EWA, WGBS) methods  | DNA modification, histone modification, miRNA expression | Identification of epigenomic variation related to disease and treatment response | Mendiola und LaSalle 2021Takeshima et al. 2020Bell et al. 2019Berdasco & Esteller 2019Placek et al. 2019Felix et al. 2018Fisel et al. 2018Linnekamp et al. 2017Fisel et al. 2016Guo et al. 2016Neul et al. 2016 Yiu und Li 2015Kacevska et al. 2012Fraga et al 2005 |
| **Transcriptomics** | RNA (tissue specific) | Targeted and untargeted (e.g. RNA seq, microarray) methods  | Individual gene expression profile | Identification of gene expression profiles related to disease and treatment response  | Scott EN et al. 2021Umans et al. 2021Mulenga et al. 2020van Groen et al. 2020Montaldo et al. 2019Shiba et al. 2019Howell et al. 2018Kessler et al. 2018Rusch et al. 2018 Wright et al. 2018Cummings et al. 2017Herberg et al. 2016Herberg et al. 2013Schröder et al. 2013Sadee et al. 2011 |
| **Proteomics** | Protein (tissue specific) | Targeted and untargeted methods (e.g. LC-MS/MS) | protein profiles | Protein biomarker development for disease and treatment | Dupree EJ et al. Proteomes. 2020Ioanna Kosteria et al. 2018Pereira-Fantini et al. 2018Wishart et al. 2018Cruz et al. 2017Froehlich et al. 2014López Villar et al. 2014Füzéry et al 2013 Saminathan et al. 2010 |
| **Metabolomics** | Metabolites (endogenous/ exogenous)  | Targeted and untargeted methods (e.g. LC-MS/MS, NMR) | Individual metabolite profiles | Identification of predictive metabolic biomarkers  | Lammers et al. 2021Moor et al. 2021Beger et al. 2020Bessey et al. 2020Estrella et al. 2020Mordaunt et al. 2020Ellul et al. 2019Everett 2019Vries et al. 2019Wang et al. 2019Coene et al. 2018Shommu et al. 2018Turi et al. 2018Vries et al. 2018Neerincx et al. 2017Trivedi et al. 2017 Dessì et al. 2014 |
| **Microbiomics** | Bacteria  | DNA/RNA sequencing, bactieria culture  | microbiomic profile | Identification of disease and treatment specific microbiomic patterns | Klünemann et al. Nature 2021Cuthbertson et al. 2020Park et al. 2020Abdel-Aziz et al. 2019Dominguez-Bello et al. 2019Fessler et al. 2019Kang et al. 2019Peirce und Alviña 2019Tuteja und Ferguson 2019Gilbert et al. 2018Hughes et al. 2018Nishida et al. 2018Nusbaum et al. 2018Man et al. 2017Silbergeld 2017Sim et al. 2015Kostic et al. 2014 Haiser & Turnbaugh 2013 |

**Table 2: Currently available CPIC Guidelines and specific paediatric recommendations**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drugs** | **Targets** | **Applicability to paediatric patients proposed**  | **Specific paediatric recommendations** |
| abacavir (Martin et al. 2014) | HLA-B | yes | no |
| allopurinol (Saito et al. 2016) | HLA-B | yes  | no |
| amikacin, gentamicin, kanamycin, paromomycin, plazomicin, streptomycin, tobramycin (McDermott et al. 2021) | MT-RNR1 | yes | yes |
| amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine (Hicks et al. 2017) | CYP2C19, CYP2D6 | yes | no |
| atazanavir (Gammal et al. 2016) | UGT1A1 | yes  | no |
| atomoxetine (Brown et al. 2019) | CYP2D6 | yes | yes |
| azathioprine, mercaptopurine, thioguanine (Relling et al. 2019) | NUDT15, TPMT | yes | yes |
| capecitabine, fluorouracil (Amstutz et al. 2018) | DPYD | yes  | no |
| carbamazepine, oxcarbazepine (Phillips et al. 2018) | HLA-A, HLA-B | yes | no |
| celecoxib, flurbiprofen, ibuprofen, lornoxicam, meloxicam, piroxicam, tenoxicam (Theken et al. 2020) | CYP2C9 | yes | no |
| citalopram, escitalopram, fluvoxamine, paroxetine, sertraline (Hicks et al. 2015) | CYP2C19 | yes for CYP2D6, for CYP2C19 with caution | no |
| clopidogrel (Scott et al. 2013) | CYP2C19 | yes  | no |
| codeine, hydrocodone, tramadol (Crews et al. 2021) | CYP2D6 | yes | advise against use of codeine (FDA and EMA) and tramadol (FDA) in children < 2 years |
| desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine (Gonsalves et al. 2019) | CACNA1S, RYR1 | no | no |
| dexlansoprazole, lansoprazole, omeprazole, pantoprazole (Lima et al. 2021) | CYP2C19 | yes | yes, only for paediatric patients >1 year |
| efavirenz (Desta et al. 2019) | CYP2B6 | yes | yes, only for paediatric patients ≥40kg body weightfor children >3 years and <40 kg body weight TDM recommended due to limited clinical data |
| fosphenytoin, phenytoin (Karnes et al. 2021) | CYP2C9, HLA-B | yes | yes, for HLA-B\*15:02,for CYP2C9 only in combination with TDM  |
| ivacaftor (Clancy et al. 2014) | CFTR | yes | yes, only for paediatric patients ≥6 years  |
| ondansetron, tropisetron (Bell et al. 2017) | CYP2D6 | no | no |
| peginterferon alfa-2a, peginterferon alfa-2b, ribavirin (Muir et al. 2014) | IFNL3 | no | no |
| rasburicase (Relling et al. 2014) | G6PD | yes | yes |
| simvastatin (Ramsey et al. 2014) | SLCO1B1 | yes | no |
| tacrolimus (Birdwell et al. 2015) | CYP3A5 | yes | yes  |
| tamoxifen (Goetz et al. 2018) | CYP2D6 | no | no |
| voriconazole (Moriyama et al. 2017) | CYP2C19 | yes | yes |
| warfarin (Johnson et al. 2017) | CYP2C9, CYP4F2, VKORC1 | yes | yes, for children of European ancestry (CYP2C9 and VKORC1) |