**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.

References

Abdel-Aziz, Mahmoud I.; Vijverberg, Susanne J. H.; Neerincx, Anne H.; Kraneveld, Aletta D.; Maitland-van der Zee, Anke H. (2019): The crosstalk between microbiome and asthma: Exploring associations and challenges. In: *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 49 (8), S. 1067–1086. DOI: 10.1111/cea.13444.

Abdullah-Koolmees, Heshu; van Keulen, Antonius M.; Nijenhuis, Marga; Deneer, Vera H. M. (2021): Pharmacogenetics Guidelines. Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines. In: *Frontiers in pharmacology* 11, S. 683. DOI: 10.3389/fphar.2020.595219.

Adam de Beaumais, Tiphaine; Jacqz-Aigrain, Evelyne (2018): Chapter Eight - Pharmacogenetics. Applications to Pediatric Patients. In: Kim Brøsen und Per Damkier (Hg.): Advances in Pharmacology : Pharmacogenetics, Bd. 83: Academic Press, S. 191–215.

Aka, Ida; Bernal, Christiana J.; Carroll, Robert; Maxwell-Horn, Angela; Oshikoya, Kazeem A.; van Driest, Sara L. (2017): Clinical Pharmacogenetics of Cytochrome P450-Associated Drugs in Children. In: *Journal of personalized medicine* 7 (4). DOI: 10.3390/jpm7040014.

Allegaert, Karel; Simons, Sinno H.P.; Tibboel, Dick; Krekels, Elke H.; Knibbe, Catherijne A.; van den Anker, John (2017): Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: Filling the gaps beyond developmental pharmacology. In: *European Journal of Pharmaceutical Sciences* (109), S. 27–31.

Amstutz, Ursula; Henricks, Linda M.; Offer, Steven M.; Barbarino, Julia; Schellens, Jan H. M.; Swen, Jesse J. et al. (2018): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. 2017 Update. In: *Clinical pharmacology and therapeutics* 103 (2), S. 210–216. DOI: 10.1002/cpt.911.

Amur, S.; LaVange, L.; Zineh, I.; Buckman-Garner, S.; Woodcock, J. (2015): Biomarker Qualification. Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. In: *Clin. Pharmacol. Ther.* 98 (1), S. 34–46. DOI: 10.1002/cpt.136.

Annalora, Andrew J.; Marcus, Craig B.; Iversen, Patrick L. (2017): Alternative Splicing in the Cytochrome P450 Superfamily Expands Protein Diversity to Augment Gene Function and Redirect Human Drug Metabolism. In: *Drug metabolism and disposition: the biological fate of chemicals* 45 (4), S. 375–389. DOI: 10.1124/dmd.116.073254.

Aslam, Bilal; Basit, Madiha; Nisar, Muhammad Atif; Khurshid, Mohsin; Rasool, Muhammad Hidayat (2017): Proteomics: Technologies and Their Applications. In: *Journal of chromatographic science* 55 (2), S. 182–196. DOI: 10.1093/chromsci/bmw167.

Baquero, F.; Nombela, C. (2012): The microbiome as a human organ. In: *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 18 Suppl 4, S. 2–4. DOI: 10.1111/j.1469-0691.2012.03916.x.

Barry, Peter J.; Mall, Marcus A.; Álvarez, Antonio; Colombo, Carla; Winter-de Groot, Karin M. de; Fajac, Isabelle et al. (2021): Triple Therapy for Cystic Fibrosis Phe508del –Gating and –Residual Function Genotypes. In: *New England Journal of Medicine* 385 (9), S. 815–825. DOI: 10.1056/NEJMoa2100665.

Beger, Richard D.; Dunn, Warwick; Schmidt, Michael A.; Gross, Steven S.; Kirwan, Jennifer A.; Cascante, Marta et al. (2016): Metabolomics enables precision medicine: "A White Paper, Community Perspective". In: *Metabolomics : Official journal of the Metabolomic Society* 12 (10), S. 149. DOI: 10.1007/s11306-016-1094-6.

Beger, Richard D.; Schmidt, Michael A.; Kaddurah-Daouk, Rima (2020): Current Concepts in Pharmacometabolomics, Biomarker Discovery, and Precision Medicine. In: *Metabolites* 10 (4), S. 129. DOI: 10.3390/metabo10040129.

Bell, Christopher G.; Lowe, Robert; Adams, Peter D.; Baccarelli, Andrea A.; Beck, Stephan; Bell, Jordana T. et al. (2019): DNA methylation aging clocks: challenges and recommendations. In: *Genome biology* 20 (1), S. 249. DOI: 10.1186/s13059-019-1824-y.

Bell, G. C.; Caudle, K. E.; Whirl-Carrillo, M.; Gordon, R. J.; Hikino, K.; Prows, C. A. et al. (2017): Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. In: *Clinical pharmacology and therapeutics* 102 (2), S. 213–218. DOI: 10.1002/cpt.598.

Berdasco, María; Esteller, Manel (2019): Clinical epigenetics: seizing opportunities for translation. In: *Nature reviews. Genetics* 20 (2), S. 109–127. DOI: 10.1038/s41576-018-0074-2.

Bessey, Alice; Chilcott, James; Pandor, Abdullah; Paisley, Suzy (2020): The Cost-Effectiveness of Expanding the UK Newborn Bloodspot Screening Programme to Include Five Additional Inborn Errors of Metabolism. In: *International journal of neonatal screening* 6 (4). DOI: 10.3390/ijns6040093.

Birdwell, K. A.; Decker, B.; Barbarino, J. M.; Peterson, J. F.; Stein, C. M.; Sadee, W. et al. (2015): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. In: *Clinical pharmacology and therapeutics* 98 (1), S. 19–24. DOI: 10.1002/cpt.113.

Brown, J. T.; Bishop, JR; Sangkuhl, K.; Nurmi, E. L.; Mueller, D. J.; Dinh, J. C. et al. (2019): Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. In: *Clinical pharmacology and therapeutics* 106 (1). DOI: 10.1002/cpt.1409.

Brown, Jacob T.; Ramsey, Laura B.; van Driest, Sara L.; Aka, Ida; Colace, Susan I. (2021): Characterizing Pharmacogenetic Testing Among Children's Hospitals. In: *Clinical and translational science* 14 (2), S. 692–701. DOI: 10.1111/cts.12931.

Burckart, Gilbert J.; Seo, Shirley; Pawlyk, Aaron C.; McCune, Susan K.; Yao, Lynne P.; Giacoia, George P. et al. (2020): Scientific and Regulatory Considerations for an Ontogeny Knowledge Base for Pediatric Clinical Pharmacology. In: *Clinical pharmacology and therapeutics* 107 (4), S. 707–709. DOI: 10.1002/cpt.1763.

Carter, Suzanne C.; McKone, Edward F. (2016): Pharmacogenetics of cystic fibrosis treatment. In: *Pharmacogenomics* 17 (13), S. 1453–1463. DOI: 10.2217/pgs.16.25.

Caspar, Sylvan Manuel; Schneider, Timo; Stoll, Patricia; Meienberg, Janine; Matyas, Gabor (2021): Potential of whole-genome sequencing-based pharmacogenetic profiling. In: *Pharmacogenomics* 22 (3), S. 177–190. DOI: 10.2217/pgs-2020-0155.

Chenoweth, Meghan J.; Giacomini, Kathleen M.; Pirmohamed, Munir; Hill, Susan L.; van Schaik, Ron H. N.; Schwab, Matthias et al. (2020): Global pharmacogenomics with precision medicine: challenges and opportunities.

Clancy, J. P.; Johnson, S. G.; Yee, S. W.; McDonagh, E. M.; Caudle, K. E.; Klein, T. E. et al. (2014): Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. In: *Clinical pharmacology and therapeutics* 95 (6), S. 592–597. DOI: 10.1038/clpt.2014.54.

Coene, Karlien L. M.; Kluijtmans, Leo A. J.; van der Heeft, Ed; Engelke, Udo F. H.; Boer, Siebolt de; Hoegen, Brechtje et al. (2018): Next-generation metabolic screening: targeted and untargeted metabolomics for the diagnosis of inborn errors of metabolism in individual patients. In: *Journal of inherited metabolic disease* 41 (3), S. 337–353. DOI: 10.1007/s10545-017-0131-6.

Crews, Kristine R.; Monte, Andrew A.; Huddart, Rachel; Caudle, Kelly E.; Kharasch, Evan D.; Gaedigk, Andrea et al. (2021): Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. In: *Clinical pharmacology and therapeutics. DOI:* 10.1002/cpt.2149.

Cruz, Isa N.; Coley, Helen M.; Kramer, Holger B.; Madhuri, Thumuluru Kavitah; Safuwan, Nur A. M.; Angelino, Ana Rita; Yang, Min (2017): Proteomics Analysis of Ovarian Cancer Cell Lines and Tissues Reveals Drug Resistance-associated Proteins. In: *Cancer genomics & proteomics* 14 (1), S. 35–51. DOI: 10.21873/cgp.20017.

Cummings, Beryl B.; Marshall, Jamie L.; Tukiainen, Taru; Lek, Monkol; Donkervoort, Sandra; Foley, A. Reghan et al. (2017): Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. In: *Science translational medicine* 9 (386). DOI: 10.1126/scitranslmed.aal5209.

Cuthbertson, Leah; Walker, Alan W.; Oliver, Anna E.; Rogers, Geraint B.; Rivett, Damian W.; Hampton, Thomas H. et al. (2020): Lung function and microbiota diversity in cystic fibrosis. In: *Microbiome* 8 (1), S. 45. DOI: 10.1186/s40168-020-00810-3.

Daly, Ann K.; Donaldson, Peter T.; Bhatnagar, Pallav; Shen, Yufeng; Pe'er, Itsik; Floratos, Aris et al. (2009): HLA-B\*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. In: *Nature genetics* 41 (7), S. 816–819. DOI: 10.1038/ng.379.

Dessì, Angelica; Cesare Marincola, Flaminia; Masili, Alice; Gazzolo, Diego; Fanos, Vassilios (2014): Clinical metabolomics and nutrition: the new frontier in neonatology and pediatrics. In: *BioMed research international* 2014, S. 981219. DOI: 10.1155/2014/981219.

Desta, Zeruesenay; Gammal, Roseann S.; Gong, Li; Whirl-Carrillo, Michelle; Gaur, Aditya H.; Sukasem, Chonlaphat et al. (2019): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. In: *Clinical pharmacology and therapeutics* 106 (4), S. 726–733. DOI: 10.1002/cpt.1477.

Diouf, Barthelemy; Crews, Kristine R.; Lew, Glen; Pei, Deqing; Cheng, Cheng; Bao, Ju et al. (2015): Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. In: *JAMA* 313 (8), S. 815–823. DOI: 10.1001/jama.2015.0894.

Dominguez-Bello, Maria Gloria; Godoy-Vitorino, Filipa; Knight, Rob; Blaser, Martin J. (2019): Role of the microbiome in human development. In: *Gut* 68 (6), S. 1108–1114. DOI: 10.1136/gutjnl-2018-317503.

Drögemöller, Britt I.; Wright, Galen E.B.; Lo, Cody; Le, Tan; Brooks, Beth; Bhavsar, Amit P. et al. (2019): Pharmacogenomics of Cisplatin‐Induced Ototoxicity. Successes, Shortcomings, and Future Avenues of Research. In: *Clin. Pharmacol. Ther.* 106 (2), S. 350–359. DOI: 10.1002/cpt.1483.

DrugBank. Online verfügbar unter www.drugbank.ca.

Dupree, Emmalyn J.; Jayathirtha, Madhuri; Yorkey, Hannah; Mihasan, Marius; Petre, Brindusa Alina; Darie, Costel C. (2020): A Critical Review of Bottom-Up Proteomics. The Good, the Bad, and the Future of This Field. In: *Proteomes* 8 (3), S. 14. DOI: 10.3390/proteomes8030014.

Ellul, Susan; Wake, Melissa; Clifford, Susan A.; Lange, Katherine; Würtz, Peter; Juonala, Markus et al. (2019): Metabolomics: population epidemiology and concordance in Australian children aged 11-12 years and their parents. In: *BMJ open* 9 (Suppl 3), S. 106–117. DOI: 10.1136/bmjopen-2017-020900.

Elzagallaai, Abdelbaset A.; Carleton, Bruce C.; Rieder, Michael J. (2021): Pharmacogenomics in Pediatric Oncology: Mitigating Adverse Drug Reactions While Preserving Efficacy. In: *Annual review of pharmacology and toxicology* 61, S. 679–699. DOI: 10.1146/annurev-pharmtox-031320-104151.

Estrella, Jane Frances Grace Lustre; Immanuel, Jincy; Wiley, Veronica; Simmons, David (2020): Newborn Screening Samples for Diabetes Research: An Underused Resource. In: *Cells* 9 (10). DOI: 10.3390/cells9102299.

Everett, Jeremy R. (2019): Pharmacometabonomics. The Prediction of Drug Effects Using Metabolic Profiling: Springer International Publishing (Concepts and Principles of Pharmacology).

Felix, Janine F.; Joubert, Bonnie R.; Baccarelli, Andrea A.; Sharp, Gemma C.; Almqvist, Catarina; Annesi-Maesano, Isabella et al. (2018): Cohort Profile: Pregnancy And Childhood Epigenetics (PACE) Consortium. In: *International journal of epidemiology* 47 (1), 22-23u. DOI: 10.1093/ije/dyx190.

Fernandez, Christian A.; Smith, Colton; Yang, Wenjian; Daté, Mihir; Bashford, Donald; Larsen, Eric et al. (2014): HLA-DRB1\*07. 01 is associated with a higher risk of asparaginase allergies. In: *Blood* 124 (8), S. 1266–1276. DOI: 10.1182/blood-2014-03-563742.

Fessler, Jessica; Matson, Vyara; Gajewski, Thomas F. (2019): Exploring the emerging role of the microbiome in cancer immunotherapy. In: *Journal for immunotherapy of cancer* 7 (1), S. 108. DOI: 10.1186/s40425-019-0574-4.

Fisel, P.; Schaeffeler, E.; Schwab, M. (2016): DNA Methylation of ADME Genes. In: *Clinical pharmacology and therapeutics* 99 (5), S. 512–527. DOI: 10.1002/cpt.343.

Fisel, Pascale; Schaeffeler, Elke; Schwab, Matthias (2018): Clinical and Functional Relevance of the Monocarboxylate Transporter Family in Disease Pathophysiology and Drug Therapy. In: *Clinical and translational science* 11 (4), S. 352–364. DOI: 10.1111/cts.12551.

Food and Drug Administration (2020): Table of Pharmacogenomic Biomarkers in Drug Labeling. Online verfügbar unter https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling#:~:text=Table%20of%20Pharmacogenomic%20Biomarkers%20in%20Drug%20Labeling%20,and%20Admini%20…%20%2023%20more%20rows, zuletzt aktualisiert am 18.08.2020, zuletzt geprüft am 31.12.2020.

Forno, Erick; Celedón, Juan C. (2019): Epigenomics and Transcriptomics in the Prediction and Diagnosis of Childhood Asthma: Are We There Yet? In: *Frontiers in pediatrics* 7, S. 115. DOI: 10.3389/fped.2019.00115.

Franca, Raffaella; Zudeh, Giulia; Lucafò, Marianna; Rabusin, Marco; Decorti, Giuliana; Stocco, Gabriele (2020): Genome wide association studies for treatment-related adverse effects of pediatric acute lymphoblastic leukemia. In: *Wiley interdisciplinary reviews. Systems biology and medicine*, e1509. DOI: 10.1002/wsbm.1509.

Froehlich, John W.; Vaezzadeh, Ali R.; Kirchner, Marc; Briscoe, Andrew C.; Hofmann, Oliver; Hide, Winston et al. (2014): An in-depth comparison of the male pediatric and adult urinary proteomes. In: *Biochimica et biophysica acta* 1844 (5), S. 1044–1050. DOI: 10.1016/j.bbapap.2013.05.008.

Fröhlich, Holger; Balling, Rudi; Beerenwinkel, Niko; Kohlbacher, Oliver; Kumar, Santosh; Lengauer, Thomas et al. (2018): From hype to reality: data science enabling personalized medicine. In: *BMC medicine* 16 (1), S. 150. DOI: 10.1186/s12916-018-1122-7.

Füzéry et al (2013): translation of proteomic biomarkers into FDA approved cancer diagnostics.

Gammal, R. S.; Court, M. H.; Haidar, C. E.; Iwuchukwu, O. F.; Gaur, A. H.; Alvarellos, M. et al. (2016): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. In: *Clinical pharmacology and therapeutics* 99 (4), S. 363–369. DOI: 10.1002/cpt.269.

Gilbert, Jack A.; Blaser, Martin J.; Caporaso, J. Gregory; Jansson, Janet K.; Lynch, Susan V.; Knight, Rob (2018): Current understanding of the human microbiome. In: *Nature medicine* 24 (4), S. 392–400. DOI: 10.1038/nm.4517.

Gliddon, Harriet D.; Herberg, Jethro A.; Levin, Michael; Kaforou, Myrsini (2018): Genome-wide host RNA signatures of infectious diseases: discovery and clinical translation. In: *Immunology* 153 (2), S. 171–178. DOI: 10.1111/imm.12841.

Goetz, Matthew P.; Sangkuhl, Katrin; Guchelaar, Henk-Jan; Schwab, Matthias; Province, Michael; Whirl-Carrillo, Michelle et al. (2018): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. In: *Clinical pharmacology and therapeutics* 103 (5), S. 770–777. DOI: 10.1002/cpt.1007.

Gonsalves, Stephen G.; Dirksen, Robert T.; Sangkuhl, Katrin; Pulk, Rebecca; Alvarellos, Maria; Vo, Teresa et al. (2019): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes. In: *Clinical pharmacology and therapeutics* 105 (6), S. 1338–1344. DOI: 10.1002/cpt.1319.

Green, Dionna (2019): Ontogeny and the Application of Pharmacogenomics to Pediatric Drug Development. In: *The Journal of Clinical Pharmacology* 59 (S1), S. 1249. DOI: 10.1002/jcph.1488.

Gregornik, David; Salyakina, Daria; Brown, Marilyn; Roiko, Samuel; Ramos, Kenneth (2021): Pediatric pharmacogenomics: challenges and opportunities: on behalf of the Sanford Children's Genomic Medicine Consortium. In: *The pharmacogenomics journal* 21 (1), S. 8–19. DOI: 10.1038/s41397-020-00181-w.

Gromova, Mariya; Vaggelas, Annegret; Dallmann, Gabriele; Seimetz, Diane (2020): Biomarkers. Opportunities and Challenges for Drug Development in the Current Regulatory Landscape. In: *BiomarkInsights* 15, 117727192097465. DOI: 10.1177/1177271920974652.

Guo, Jia; Johansson, Inger; Mkrtchian, Souren; Ingelman-Sundberg, Magnus (2016): The CYP2W1 enzyme: regulation, properties and activation of prodrugs. In: *Drug metabolism reviews* 48 (3), S. 369–378. DOI: 10.1080/03602532.2016.1188939.

Haiser, Henry J.; Turnbaugh, Peter J. (2013): Developing a metagenomic view of xenobiotic metabolism. In: *Pharmacological research* 69 (1), S. 21–31. DOI: 10.1016/j.phrs.2012.07.009.

Hanna, Mina H.; Brophy, Patrick D. (2015): Metabolomics in pediatric nephrology: emerging concepts. In: *Pediatric nephrology (Berlin, Germany)* 30 (6), S. 881–887. DOI: 10.1007/s00467-014-2880-x.

Hawcutt, Daniel B.; Thompson, Ben; Smyth, Rosalind L.; Pirmohamed, Munir (2013): Paediatric pharmacogenomics: an overview. In: *Archives of disease in childhood* 98 (3), S. 232–237. DOI: 10.1136/archdischild-2012-302852.

Herberg, Jethro A.; Kaforou, Myrsini; Gormley, Stuart; Sumner, Edward R.; Patel, Sanjay; Jones, Kelsey D. J. et al. (2013): Transcriptomic profiling in childhood H1N1/09 influenza reveals reduced expression of protein synthesis genes. In: *The Journal of infectious diseases* 208 (10), S. 1664–1668. DOI: 10.1093/infdis/jit348.

Herberg, Jethro A.; Kaforou, Myrsini; Wright, Victoria J.; Shailes, Hannah; Eleftherohorinou, Hariklia; Hoggart, Clive J. et al. (2016): Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children. In: *JAMA* 316 (8), S. 835–845. DOI: 10.1001/jama.2016.11236.

Hicks, J. K.; Bishop, J. R.; Sangkuhl, K.; Müller, D. J.; Ji, Y.; Leckband, S. G. et al. (2015): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. In: *Clinical pharmacology and therapeutics* 98 (2), S. 127–134. DOI: 10.1002/cpt.147.

Hicks, J. K.; Sangkuhl, K.; Swen, J. J.; Ellingrod, V. L.; Müller, D. J.; Shimoda, K. et al. (2017): Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. 2016 update. In: *Clinical pharmacology and therapeutics* 102 (1), S. 37–44. DOI: 10.1002/cpt.597.

Howell, Kate Joanne; Kraiczy, Judith; Nayak, Komal M.; Gasparetto, Marco; Ross, Alexander; Lee, Claire et al. (2018): DNA Methylation and Transcription Patterns in Intestinal Epithelial Cells From Pediatric Patients With Inflammatory Bowel Diseases Differentiate Disease Subtypes and Associate With Outcome. In: *Gastroenterology* 154 (3), S. 585–598. DOI: 10.1053/j.gastro.2017.10.007.

Hughes, Heather K.; Rose, Destanie; Ashwood, Paul (2018): The Gut Microbiota and Dysbiosis in Autism Spectrum Disorders. In: *Current neurology and neuroscience reports* 18 (11), S. 81. DOI: 10.1007/s11910-018-0887-6.

ICH Expert Working Group: ICH Harmonised Tripartite Guideline: Biomarkers related to drug or biotechnology product development: context, structure and format of qualification submissions E16. Current Step 4 version, dated 20 August 2010. Online verfügbar unter https://database.ich.org/sites/default/files/E16\_Guideline.pdf.

IMI: conect4children. Online verfügbar unter https://www.imi.europa.eu/projects-results/project-factsheets/c4c, zuletzt geprüft am 26.04.2021.

Ioanna Kosteria; Christina Kanaka-Gantenbein; Athanasios K. Anagnostopoulos; George P. Chrousos; George Th. Tsangaris (2018): Pediatric endocrine and metabolic diseases and proteomics. In: *Journal of Proteomics* (188), Pages 46-58. DOI: 10.1016/j.jprot.2018.03.011.

Johnson, Danielle; Hughes, Dyfrig; Pirmohamed, Munir; Jorgensen, Andrea (2019): Evidence to Support Inclusion of Pharmacogenetic Biomarkers in Randomised Controlled Trials. In: *Journal of personalized medicine* 9 (3). DOI: 10.3390/jpm9030042.

Johnson, J. A.; Caudle, K. E.; Gong, L.; Whirl-Carrillo, M.; Stein, C. M.; Scott, S. A. et al. (2017): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing. 2017 Update. In: *Clinical pharmacology and therapeutics* 102 (3), S. 397–404. DOI: 10.1002/cpt.668.

Kacevska, Marina; Ivanov, Maxim; Wyss, Annika; Kasela, Silva; Milani, Lili; Rane, Anders; Ingelman-Sundberg, Magnus (2012): DNA methylation dynamics in the hepatic CYP3A4 gene promoter. In: *Biochimie* 94 (11), S. 2338–2344. DOI: 10.1016/j.biochi.2012.07.013.

Kang, Dae-Wook; Adams, James B.; Coleman, Devon M.; Pollard, Elena L.; Maldonado, Juan; McDonough-Means, Sharon et al. (2019): Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. In: *Scientific reports* 9 (1), S. 5821. DOI: 10.1038/s41598-019-42183-0.

Karnes, Jason H.; Rettie, Allan E.; Somogyi, Andrew A.; Huddart, Rachel; Fohner, Alison E.; Formea, Christine M. et al. (2021): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing. 2020 Update. In: *Clinical pharmacology and therapeutics* 109 (2), S. 302–309. DOI: 10.1002/cpt.2008.

Kearns Gregory L.; Abdel-Rahman Susan M.; Alander Sarah W.; Blowey Douglas L.; Leeder J. Steven; Kauffman Ralph E. (2003): Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. In: *New England Journal of Medicine*, S. 1157–1167.

Kessler, Haeja; Jiang, Kaiyu; Jarvis, James N. (2018): Using Chromatin Architecture to Understand the Genetics and Transcriptomics of Juvenile Idiopathic Arthritis. In: *Frontiers in immunology* 9, S. 2964. DOI: 10.3389/fimmu.2018.02964.

Klünemann, Martina; Andrejev, Sergej; Blasche, Sonja; Mateus, Andre; Phapale, Prasad; Devendran, Saravanan et al. (2021): Bioaccumulation of therapeutic drugs by human gut bacteria. In: *Nature* 597 (7877), S. 533–538. DOI: 10.1038/s41586-021-03891-8.

Kostic, Aleksandar D.; Xavier, Ramnik J.; Gevers, Dirk (2014): The microbiome in inflammatory bowel disease: current status and the future ahead. In: *Gastroenterology* 146 (6), S. 1489–1499. DOI: 10.1053/j.gastro.2014.02.009.

Kovar, Lukas; Schräpel, Christina; Selzer, Dominik; Kohl, Yvonne; Bals, Robert; Schwab, Matthias; Lehr, Thorsten (2020): Physiologically-Based Pharmacokinetic (PBPK) Modeling of Buprenorphine in Adults, Children and Preterm Neonates. In: *Pharmaceutics* 12 (6). DOI: 10.3390/pharmaceutics12060578.

Krebs, Kristi; Milani, Lili (2019): Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. In: *Human genomics* 13 (1), S. 39. DOI: 10.1186/s40246-019-0229-z.

Lammers, Ariana; Brinkman, Paul; Te Nijenhuis, LouwrinaH; Vries, Rianne de; Dagelet, Yennece W. F.; Duijvelaar, Erik et al. (2021): Increased day-to-day fluctuations in exhaled breath profiles aftera rhinovirus challenge in asthma. In: *Allergy. DOI:* 10.1111/all.14811.

Lee, Jong W.; Pussegoda, Kusala; Rassekh, Shahrad R.; Monzon, Jose G.; Liu, Geoffrey; Hwang, Soomi et al. (2016): Clinical Practice Recommendations for the Management and Prevention of Cisplatin-Induced Hearing Loss Using Pharmacogenetic Markers. In: *Therapeutic drug monitoring* 38 (4), S. 423–431. DOI: 10.1097/FTD.0000000000000298.

Liang, Zhixian; Kidwell, Reilly L.; Deng, Haijing; Xie, Qi (2020): Epigenetic N6-methyladenosine modification of RNA and DNA regulates cancer. In: *Cancer biology & medicine* 17 (1), S. 9–19. DOI: 10.20892/j.issn.2095-3941.2019.0347.

Lima, John J.; Thomas, Cameron D.; Barbarino, Julia; Desta, Zeruesenay; van Driest, Sara L.; El Rouby, Nihal et al. (2021): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. In: *Clinical pharmacology and therapeutics* 109 (6), S. 1417–1423. DOI: 10.1002/cpt.2015.

~~Linnekamp, J. F.; Butter, R.; Spijker, R.; Medema, J. P.; van Laarhoven, H. W. M. (2017): Clinical and biological effects of demethylating agents on solid tumours - A systematic review. In:~~ *~~Cancer treatment reviews~~* ~~54, S. 10–23. DOI: 10.1016/j.ctrv.2017.01.004.~~

Lonergan, Mike; Senn, Stephen J.; McNamee, Christine; Daly, Ann K.; Sutton, Robert; Hattersley, Andrew et al. (2017): Defining drug response for stratified medicine. In: *Drug Discovery Today* 22 (1), S. 173–179. DOI: 10.1016/j.drudis.2016.10.016.

López Villar, Elena; Wu, Duojiao; Cho, William C.; Madero, Luis; Wang, Xiangdong (2014): Proteomics-based discovery of biomarkers for paediatric acute lymphoblastic leukaemia: challenges and opportunities. In: *Journal of cellular and molecular medicine* 18 (7), S. 1239–1246. DOI: 10.1111/jcmm.12319.

Maagdenberg, Hedy; Vijverberg, Susanne J. H.; Bierings, Marc B.; Carleton, Bruce C.; Arets, Hubertus G. M.; Boer, Anthonius de; Maitland-van der Zee, Anke H. (2016): Pharmacogenomics in Pediatric Patients: Towards Personalized Medicine. In: *Paediatric drugs* 18 (4), S. 251–260. DOI: 10.1007/s40272-016-0176-2.

Man, Wing Ho; Steenhuijsen Piters, Wouter A. A. de; Bogaert, Debby (2017): The microbiota of the respiratory tract: gatekeeper to respiratory health. In: *Nature reviews. Microbiology* 15 (5), S. 259–270. DOI: 10.1038/nrmicro.2017.14.

Mario F. Fraga et al (2005): Epigenetic differnces arise during the lifetime of monozygotic twins.

Martin, M. A.; Hoffman, J. M.; Freimuth, R. R.; Klein, T. E.; Dong, B. J.; Pirmohamed, M. et al. (2014): Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing. 2014 update. In: *Clinical pharmacology and therapeutics* 95 (5), S. 499–500. DOI: 10.1038/clpt.2014.38.

McDermott, J. H.; Wolf, J.; Hoshitsuki, K.; Huddart, R.; Caudle, K. E.; Whirl-Carrillo, M. et al. (2021): Clinical Pharmacogenetics Implementation Consortium Guideline for the Use of Aminoglycosides Based on MT-RNR1 Genotype. In: *Clinical pharmacology and therapeutics. DOI:* 10.1002/cpt.2309.

Mendiola, Aron Judd P.; LaSalle, Janine M. (2021): Epigenetics in Prader-Willi Syndrome. In: *Frontiers in genetics* 12, S. 624581. DOI: 10.3389/fgene.2021.624581.

Meyer, Urs A.; Zanger, Ulrich M.; Schwab, Matthias (2013): Omics and Drug Response. In: *Annu. Rev. Pharmacol. Toxicol.* 53 (1), S. 475–502. DOI: 10.1146/annurev-pharmtox-010510-100502.

Montaldo, Paolo; Kaforou, Myrsini; Pollara, Gabriele; Hervás-Marín, David; Calabria, Ines; Panadero, Joaquin et al. (2019): Whole Blood Gene Expression Reveals Specific Transcriptome Changes in Neonatal Encephalopathy. In: *Neonatology* 115 (1), S. 68–76. DOI: 10.1159/000492420.

Moor, Catharina C.; Oppenheimer, Judith C.; Nakshbandi, Gizal; Aerts, Joachim G. J. V.; Brinkman, Paul; Maitland-van der Zee, Anke-Hilse; Wijsenbeek, Marlies S. (2021): Exhaled breath analysis by use of eNose technology: a novel diagnostic tool for interstitial lung disease. In: *The European respiratory journal* 57 (1). DOI: 10.1183/13993003.02042-2020.

Mordaunt, Dylan; Cox, David; Fuller, Maria (2020): Metabolomics to Improve the Diagnostic Efficiency of Inborn Errors of Metabolism. In: *IJMS* 21 (4), S. 1195. DOI: 10.3390/ijms21041195.

Moriyama, B.; Obeng, A. Owusu; Barbarino, J.; Penzak, S. R.; Henning, S. A.; Scott, S. A. et al. (2017): Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. In: *Clinical pharmacology and therapeutics* 102 (1), S. 45–51. DOI: 10.1002/cpt.583.

Muir, A. J.; Gong, L.; Johnson, S. G.; Lee, M. T. M.; Williams, M. S.; Klein, T. E. et al. (2014): Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and PEG interferon-α-based regimens. In: *Clinical pharmacology and therapeutics* 95 (2), S. 141–146. DOI: 10.1038/clpt.2013.203.

Mulenga, Humphrey; Zauchenberger, Chambrez-Zita; Bunyasi, Erick W.; Mbandi, Stanley Kimbung; Mendelsohn, Simon C.; Kagina, Benjamin et al. (2020): Performance of diagnostic and predictive host blood transcriptomic signatures for Tuberculosis disease: A systematic review and meta-analysis. In: *PloS one* 15 (8), e0237574. DOI: 10.1371/journal.pone.0237574.

Neavin, Drew; Kaddurah-Daouk, Rima; Weinshilboum, Richard (2016): Pharmacometabolomics informs pharmacogenomics. In: *Metabolomics : Official journal of the Metabolomic Society* 12 (7), S. 17. DOI: 10.1007/s11306-016-1066-x.

Neerincx, Anne H.; Vijverberg, Susanne J. H.; Bos, Lieuwe D. J.; Brinkman, Paul; van der Schee, Marc P.; Vries, Rianne de et al. (2017): Breathomics from exhaled volatile organic compounds in pediatric asthma. In: *Pediatric pulmonology* 52 (12), S. 1616–1627. DOI: 10.1002/ppul.23785.

Neul, Claudia; Schaeffeler, Elke; Sparreboom, Alex; Laufer, Stefan; Schwab, Matthias; Nies, Anne T. (2016): Impact of Membrane Drug Transporters on Resistance to Small-Molecule Tyrosine Kinase Inhibitors. In: *Trends in pharmacological sciences* 37 (11), S. 904–932. DOI: 10.1016/j.tips.2016.08.003.

Nicoletti, P.; Carr, D. F.; Barrett, S.; McEvoy, L.; Friedmann, P. S.; Shear, N. H. et al. (2021): Beta-lactam-induced immediate hypersensitivity reactions. A genome-wide association study of a deeply phenotyped cohort. In: *The Journal of allergy and clinical immunology* 147 (5). DOI: 10.1016/j.jaci.2020.10.004.

Nishida, Atsushi; Inoue, Ryo; Inatomi, Osamu; Bamba, Shigeki; Naito, Yuji; Andoh, Akira (2018): Gut microbiota in the pathogenesis of inflammatory bowel disease. In: *Clinical journal of gastroenterology* 11 (1), S. 1–10. DOI: 10.1007/s12328-017-0813-5.

Nusbaum, David J.; Sun, Fengzhu; Ren, Jie; Zhu, Zifan; Ramsy, Natalie; Pervolarakis, Nicholas et al. (2018): Gut microbial and metabolomic profiles after fecal microbiota transplantation in pediatric ulcerative colitis patients. In: *FEMS microbiology ecology* 94 (9). DOI: 10.1093/femsec/fiy133.

Ortiz-Barahona V.; Joshi R. S.; Esteller M. (2020): Use of DNA methylation profiling in translational oncology. In: *Seminars in Cancer Biology*.

Osanlou, Orod; Pirmohamed, Munir; Daly, Ann K. (2018): Chapter Seven - Pharmacogenetics of Adverse Drug Reactions. In: Kim Brøsen und Per Damkier (Hg.): Advances in Pharmacology : Pharmacogenetics, Bd. 83: Academic Press, S. 155–190.

Pang, Huanhuan; Jia, Wei; Hu, Zeping (2019): Emerging Applications of Metabolomics in Clinical Pharmacology. In: *Clinical pharmacology and therapeutics* 106 (3), S. 544–556. DOI: 10.1002/cpt.1538.

Park, Il-Ho; Lee, Joong Seob; Park, Joo-Hoo; Kang, Sung Hun; Hong, Seok Min; Park, Il Seok et al. (2020): Comparison of the human microbiome in adults and children with chronic rhinosinusitis. In: *PloS one* 15 (12), e0242770. DOI: 10.1371/journal.pone.0242770.

Paul, Steven M.; Mytelka, Daniel S.; Dunwiddie, Christopher T.; Persinger, Charles C.; Munos, Bernard H.; Lindborg, Stacy R.; Schacht, Aaron L. (2010): How to improve R&D productivity. The pharmaceutical industry's grand challenge. In: *Nat Rev Drug Discov* 9 (3), S. 203–214. DOI: 10.1038/nrd3078.

Peirce, Jason M.; Alviña, Karina (2019): The role of inflammation and the gut microbiome in depression and anxiety. In: *Journal of neuroscience research* 97 (10), S. 1223–1241. DOI: 10.1002/jnr.24476.

Pereira-Fantini, Prue M.; Byars, Sean G.; McCall, Karen E.; Perkins, Elizabeth J.; Oakley, Regina B.; Dellacà, R. L. et al. (2018): Plasma proteomics reveals gestational age-specific responses to mechanical ventilation and identifies the mechanistic pathways that initiate preterm lung injury. In: *Scientific reports* 8 (1), S. 12616. DOI: 10.1038/s41598-018-30868-x.

PharmGKB: Pharmakogenomic Knowledge Base. Online verfügbar unter https://www.pharmgkb.org/, zuletzt geprüft am 14.04.2021.

Phillips, Elizabeth J.; Sukasem, Chonlaphat; Whirl-Carrillo, Michelle; Müller, Daniel J.; Dunnenberger, Henry M.; Chantratita, Wasun et al. (2018): Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine. 2017 Update. In: *Clinical pharmacology and therapeutics* 103 (4), S. 574–581. DOI: 10.1002/cpt.1004.

Placek, Katarzyna; Schultze, Joachim L.; Aschenbrenner, Anna C. (2019): Epigenetic reprogramming of immune cells in injury, repair, and resolution. In: *The Journal of clinical investigation* 129 (8), S. 2994–3005. DOI: 10.1172/JCI124619.

Rahawi, Shahad; Naik, Hetanshi; Blake, Kathryn V.; Owusu Obeng, Aniwaa; Wasserman, Rachel M.; Seki, Yoshinori et al. (2020): Knowledge and attitudes on pharmacogenetics among pediatricians. In: *Journal of human genetics* 65 (5), S. 437–444. DOI: 10.1038/s10038-020-0723-0.

Ramsey, L. B.; Johnson, S. G.; Caudle, K. E.; Haidar, C. E.; Voora, D.; Wilke, R. A. et al. (2014): The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy. 2014 update. In: *Clinical pharmacology and therapeutics* 96 (4), S. 423–428. DOI: 10.1038/clpt.2014.125.

Ramsey, Laura B.; Brown, Jacob T.; Vear, Susan I.; Bishop, Jeffrey R.; van Driest, Sara L. (2020): Gene-Based Dose Optimization in Children. In: *Annual review of pharmacology and toxicology* 60, S. 311–331. DOI: 10.1146/annurev-pharmtox-010919-023459.

Relling, M. V.; McDonagh, E. M.; Chang, T.; Caudle, K. E.; McLeod, H. L.; Haidar, C. E. et al. (2014): Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. In: *Clinical pharmacology and therapeutics* 96 (2), S. 169–174. DOI: 10.1038/clpt.2014.97.

Relling, Mary V.; Schwab, Matthias; Whirl-Carrillo, Michelle; Suarez-Kurtz, Guilherme; Pui, Ching-Hon; Stein, Charles M. et al. (2019): Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. In: *Clinical pharmacology and therapeutics* 105 (5), S. 1095–1105. DOI: 10.1002/cpt.1304.

Roberts, Timothy A.; Wagner, Jennifer A.; Sandritter, Tracy; Black, Benjamin T.; Gaedigk, Andrea; Stancil, Stephani L. (2021): Retrospective Review of Pharmacogenetic Testing at an Academic Children's Hospital. In: *Clinical and translational science* 14 (1), S. 412–421. DOI: 10.1111/cts.12895.

Rusch, Michael; Nakitandwe, Joy; Shurtleff, Sheila; Newman, Scott; Zhang, Zhaojie; Edmonson, Michael N. et al. (2018): Clinical cancer genomic profiling by three-platform sequencing of whole genome, whole exome and transcriptome. In: *Nature communications* 9 (1), S. 3962. DOI: 10.1038/s41467-018-06485-7.

Sadee, W.; Wang, D.; Papp, A. C.; Pinsonneault, J. K.; Smith, R. M.; Moyer, R. A.; Johnson, A. D. (2011): Pharmacogenomics of the RNA world: structural RNA polymorphisms in drug therapy. In: *Clinical pharmacology and therapeutics* 89 (3), S. 355–365. DOI: 10.1038/clpt.2010.314.

Saito, Y.; Stamp, L. K.; Caudle, K. E.; Hershfield, M. S.; McDonagh, E. M.; Callaghan, J. T. et al. (2016): Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing. 2015 update. In: *Clinical pharmacology and therapeutics* 99 (1), S. 36–37. DOI: 10.1002/cpt.161.

Saminathan, Ramasamy; Bai, Jing; Sadrolodabaee, Laleh; Karthik, Govindasamy Muralidharan; Singh, Onkar; Subramaniyan, Koilan et al. (2010): VKORC1 pharmacogenetics and pharmacoproteomics in patients on warfarin anticoagulant therapy: transthyretin precursor as a potential biomarker. In: *PloS one* 5 (12), e15064. DOI: 10.1371/journal.pone.0015064.

Schaeffeler, Elke; Jaeger, Simon U.; Klumpp, Verena; Yang, Jun J.; Igel, Svitlana; Hinze, Laura et al. (2019): Impact of NUDT15 genetics on severe thiopurine-related hematotoxicity in patients with European ancestry. In: *Genetics in medicine : official journal of the American College of Medical Genetics* 21 (9), S. 2145–2150. DOI: 10.1038/s41436-019-0448-7.

Schröder, A.; Klein, K.; Winter, S.; Schwab, M.; Bonin, M.; Zell, A.; Zanger, U. M. (2013): Genomics of ADME gene expression: mapping expression quantitative trait loci relevant for absorption, distribution, metabolism and excretion of drugs in human liver. In: *The pharmacogenomics journal* 13 (1), S. 12–20. DOI: 10.1038/tpj.2011.44.

Scott, E. N.; Wright, G. E.B.; Drögemöller, B. I.; Hasbullah, J. S.; Gunaretnam, E. P.; Miao, F. et al. (2021): Transcriptome-wide association study uncovers the role of essential genes in anthracycline-induced cardiotoxicity. In: *NPJ genomic medicine* 6 (1). DOI: 10.1038/s41525-021-00199-4.

Scott, S. A.; Sangkuhl, K.; Stein, C. M.; Hulot, J-S; Mega, J. L.; Roden, D. M. et al. (2013): Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy. 2013 update. In: *Clinical pharmacology and therapeutics* 94 (3), S. 317–323. DOI: 10.1038/clpt.2013.105.

Shah, Rashmi R.; Smith, Robert L. (2015): Addressing phenoconversion: the Achilles' heel of personalized medicine. In: *British journal of clinical pharmacology* 79 (2), S. 222–240. DOI: 10.1111/bcp.12441.

Shiba, Norio; Yoshida, Kenichi; Hara, Yusuke; Yamato, Genki; Shiraishi, Yuichi; Matsuo, Hidemasa et al. (2019): Transcriptome analysis offers a comprehensive illustration of the genetic background of pediatric acute myeloid leukemia. In: *Blood advances* 3 (20), S. 3157–3169. DOI: 10.1182/bloodadvances.2019000404.

Shommu, Nusrat S.; Jenne, Craig N.; Blackwood, Jaime; Martin, Dori-Ann; Joffe, Ari R.; Eccles, Robin et al. (2018): The Use of Metabolomics and Inflammatory Mediator Profiling Provides a Novel Approach to Identifying Pediatric Appendicitis in the Emergency Department. In: *Scientific reports* 8 (1), S. 4083. DOI: 10.1038/s41598-018-22338-1.

Silbergeld, Ellen K. (2017): The Microbiome. In: *Toxicologic pathology* 45 (1), S. 190–194. DOI: 10.1177/0192623316672073.

Sim, Kathleen; Shaw, Alexander G.; Randell, Paul; Cox, Michael J.; McClure, Zoë E.; Li, Ming-Shi et al. (2015): Dysbiosis anticipating necrotizing enterocolitis in very premature infants. In: *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 60 (3), S. 389–397. DOI: 10.1093/cid/ciu822.

Sing, Chor-Wing; Cheung, Ching-Lung; Wong, Ian C. K. (2015): Pharmacogenomics--how close/far are we to practising individualized medicine for children? In: *British journal of clinical pharmacology* 79 (3), S. 419–428. DOI: 10.1111/bcp.12338.

Stevens, Adam; Leonibus, Chiara de; Hanson, Daniel; Whatmore, Andrew; Murray, Philip; Donn, Rachelle et al. (2013): Pediatric perspective on pharmacogenomics. In: *Pharmacogenomics* 14 (15), S. 1889–1905. DOI: 10.2217/pgs.13.193.

~~Takeshima, Hideyuki; Yoda, Yukie; Wakabayashi, Mika; Hattori, Naoko; Yamashita, Satoshi; Ushijima, Toshikazu (2020): Low-dose DNA demethylating therapy induces reprogramming of diverse cancer-related pathways at the single-cell level. In:~~ *~~Clinical epigenetics~~* ~~12 (1), S. 142. DOI: 10.1186/s13148-020-00937-y.~~

Theken, K. N.; Lee, C. R.; Gong, L.; Caudle, K. E.; Formea, C. M.; Gaedigk, A. et al. (2020): Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. In: *Clinical pharmacology and therapeutics* 108 (2). DOI: 10.1002/cpt.1830.

Trivedi, Drupad K.; Hollywood, Katherine A.; Goodacre, Royston (2017): Metabolomics for the masses: The future of metabolomics in a personalized world. In: *New horizons in translational medicine* 3 (6), S. 294–305. DOI: 10.1016/j.nhtm.2017.06.001.

Turi, Kedir N.; Romick-Rosendale, Lindsey; Ryckman, Kelli K.; Hartert, Tina V. (2018): A review of metabolomics approaches and their application in identifying causal pathways of childhood asthma. In: *The Journal of allergy and clinical immunology* 141 (4), S. 1191–1201. DOI: 10.1016/j.jaci.2017.04.021.

Tuteja, Sony; Ferguson, Jane F. (2019): Gut Microbiome and Response to Cardiovascular Drugs. In: *Circulation. Genomic and precision medicine* 12 (9), S. 421–429. DOI: 10.1161/CIRCGEN.119.002314.

Umans, B. D.; Battle, A.; Gilad, Y. (2021): Where Are the Disease-Associated eQTLs? In: *Trends in Genetics* (37), Pages 109-124. DOI: 10.1016/j.tig.2020.08.009.

van den Anker, John; Reed, Michael D.; Allegaert, Karel; Kearns, Gregory L. (2018): Developmental Changes in Pharmacokinetics and Pharmacodynamics. In: *Journal of clinical pharmacology* 58 Suppl 10, S10-S25. DOI: 10.1002/jcph.1284.

van Groen, Bianca D.; Bi, Chengpeng; Gaedigk, Roger; Staggs, Vincent S.; Tibboel, Dick; Wildt, Saskia N. de; Leeder, J. Steven (2020): Alternative Splicing of the SLCO1B1 Gene: An Exploratory Analysis of Isoform Diversity in Pediatric Liver. In: *Clinical and translational science* 13 (3), S. 509–519. DOI: 10.1111/cts.12733.

van Paemel, Ruben; Vlug, Roos; Preter, Katleen de; van Roy, Nadine; Speleman, Frank; Willems, Leen et al. (2020): The pitfalls and promise of liquid biopsies for diagnosing and treating solid tumors in children: a review. In: *European journal of pediatrics* 179 (2), S. 191–202. DOI: 10.1007/s00431-019-03545-y.

Verscheijden, Laurens F. M.; Koenderink, Jan B.; Johnson, Trevor N.; Wildt, Saskia N. de; Russel, Frans G. M. (2020): Physiologically-based pharmacokinetic models for children: Starting to reach maturation? In: *Pharmacology & therapeutics* 211, S. 107541. DOI: 10.1016/j.pharmthera.2020.107541.

Vries, R. de; Muller, M.; van der Noort, V.; Theelen, W. S. M. E.; Schouten, R. D.; Hummelink, K. et al. (2019): Prediction of response to anti-PD-1 therapy in patients with non-small-cell lung cancer by electronic nose analysis of exhaled breath. In: *Annals of oncology : official journal of the European Society for Medical Oncology* 30 (10), S. 1660–1666. DOI: 10.1093/annonc/mdz279.

Vries, Rianne de; Dagelet, Yennece W. F.; Spoor, Pien; Snoey, Erik; Jak, Patrick M. C.; Brinkman, Paul et al. (2018): Clinical and inflammatory phenotyping by breathomics in chronic airway diseases irrespective of the diagnostic label. In: *The European respiratory journal* 51 (1). DOI: 10.1183/13993003.01817-2017.

Wang, Eric T.; Sandberg, Rickard; Luo, Shujun; Khrebtukova, Irina; Zhang, Lu; Mayr, Christine et al. (2008): Alternative isoform regulation in human tissue transcriptomes. In: *Nature* 456 (7221), S. 470–476. DOI: 10.1038/nature07509.

Wang, Xinzhu; Nijman, Ruud; Camuzeaux, Stephane; Sands, Caroline; Jackson, Heather; Kaforou, Myrsini et al. (2019): Plasma lipid profiles discriminate bacterial from viral infection in febrile children. In: *Scientific reports* 9 (1), S. 17714. DOI: 10.1038/s41598-019-53721-1.

Wilson, Ian D.; Nicholson, Jeremy K. (2017): Gut microbiome interactions with drug metabolism, efficacy, and toxicity. In: *Translational research : the journal of laboratory and clinical medicine* 179, S. 204–222. DOI: 10.1016/j.trsl.2016.08.002.

Wishart, David S.; Feunang, Yannick D.; Guo, An C.; Lo, Elvis J.; Marcu, Ana; Grant, Jason R. et al. (2018): DrugBank 5.0: a major update to the DrugBank database for 2018. In: *Nucleic acids research* 46 (D1), D1074-D1082. DOI: 10.1093/nar/gkx1037.

Wojtyniak, Jan-Georg; Britz, Hannah; Selzer, Dominik; Schwab, Matthias; Lehr, Thorsten (2020): Data Digitizing: Accurate and Precise Data Extraction for Quantitative Systems Pharmacology and Physiologically-Based Pharmacokinetic Modeling. In: *CPT: pharmacometrics & systems pharmacology* 9 (6), S. 322–331. DOI: 10.1002/psp4.12511.

Wojtyniak, Jan-Georg; Selzer, Dominik; Schwab, Matthias; Lehr, Thorsten (2021): Physiologically Based Precision Dosing Approach for Drug-Drug-Gene Interactions: A Simvastatin Network Analysis. In: *Clinical pharmacology and therapeutics* 109 (1), S. 201–211. DOI: 10.1002/cpt.2111.

Wright, Galen E. B.; Amstutz, Ursula; Drögemöller, Britt I.; Shih, Joanne; Rassekh, Shahrad R.; Hayden, Michael R. et al. (2019): Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy Implicates Pharmacokinetic and Inherited Neuropathy Genes. In: *Clinical pharmacology and therapeutics* 105 (2), S. 402–410. DOI: 10.1002/cpt.1179.

Wright, Victoria J.; Herberg, Jethro A.; Kaforou, Myrsini; Shimizu, Chisato; Eleftherohorinou, Hariklia; Shailes, Hannah et al. (2018): Diagnosis of Kawasaki Disease Using a Minimal Whole-Blood Gene Expression Signature. In: *JAMA pediatrics* 172 (10), e182293. DOI: 10.1001/jamapediatrics.2018.2293.

Yiu, Teresa T.; Li, Wei (2015): Pediatric cancer epigenome and the influence of folate. In: *Epigenomics* 7 (6), S. 961–973. DOI: 10.2217/epi.15.42.

Zanger, Ulrich M.; Schwab, Matthias (2013): Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. In: *Pharmacology & therapeutics* 138 (1), S. 103–141. DOI: 10.1016/j.pharmthera.2012.12.007.

Zhang, Jian; Zhang, Yi-Zhe; Jiang, Jing; Duan, Cheng-Guo (2020): The Crosstalk Between Epigenetic Mechanisms and Alternative RNA Processing Regulation. In: *Frontiers in genetics* 11, S. 998. DOI: 10.3389/fgene.2020.00998.

Zhao, Boxuan Simen; Roundtree, Ian A.; He, Chuan (2017): Post-transcriptional gene regulation by mRNA modifications. In: *Nature reviews. Molecular cell biology* 18 (1), S. 31–42. DOI: 10.1038/nrm.2016.132.

**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. 2021  Barry et al. 2021  Caspar et al. 2021  McDermott et al. 2021  Nicoletti et al. 2021  Franca et al. 2020  Brown et al. 2019  Drögemöller et al. 2019  Relling et al. 2019  Schaeffeler et al. 2019  Wright et al. 2019  Carter & McKone 2016  Lee JW et al. 2016  Birdwell et al. 2015  Diouf et al. 2015  Fernandez *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 2021  Takeshima et al. 2020  Bell et al. 2019  Berdasco & Esteller 2019  Placek et al. 2019  Felix et al. 2018  Fisel et al. 2018  Linnekamp et al. 2017  Fisel et al. 2016  Guo et al. 2016  Neul et al. 2016  Yiu und Li 2015  Kacevska et al. 2012  Fraga 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. 2021  Umans et al. 2021  Mulenga et al. 2020  van Groen et al. 2020  Montaldo et al. 2019  Shiba et al. 2019  Howell et al. 2018  Kessler et al. 2018  Rusch et al. 2018  Wright et al. 2018  Cummings et al. 2017  Herberg et al. 2016  Herberg et al. 2013  Schröder et al. 2013  Sadee 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. 2020  Ioanna Kosteria et al. 2018  Pereira-Fantini et al. 2018  Wishart et al. 2018  Cruz et al. 2017  Froehlich et al. 2014  López Villar et al. 2014  Füzéry 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. 2021  Moor et al. 2021  Beger et al. 2020  Bessey et al. 2020  Estrella et al. 2020  Mordaunt et al. 2020  Ellul et al. 2019  Everett 2019  Vries et al. 2019  Wang et al. 2019  Coene et al. 2018  Shommu et al. 2018  Turi et al. 2018  Vries et al. 2018  Neerincx et al. 2017  Trivedi 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 2021  Cuthbertson et al. 2020  Park et al. 2020  Abdel-Aziz et al. 2019  Dominguez-Bello et al. 2019  Fessler et al. 2019  Kang et al. 2019  Peirce und Alviña 2019  Tuteja und Ferguson 2019  Gilbert et al. 2018  Hughes et al. 2018  Nishida et al. 2018  Nusbaum et al. 2018  Man et al. 2017  Silbergeld 2017  Sim et al. 2015  Kostic 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 weight  for 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) |