Received: 30 April 2021 | Revised: 11 December 2021 | Accepted: 14 December 2021

DOI: 10.1111/bcp.15216

THEMED ISSUE REVIEW

How paediatric drug development and use could benefit from OMICs: A c4c expert group white paper

Eva Neumann[1] | Filippa Schreeck[1] | Jethro Herberg[2] | Evelyne Jacqz Aigrain[3,4,5] | Anke H. Maitland-van der Zee[6] | Antonio Pérez-Martínez[7,8,9] | Daniel B. Hawcutt[10,11] | Elke Schaeffeler[1] | Anders Rane[12] | Saskia N. de Wildt[13,14] | Matthias Schwab[1,15]

[1]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, and University of Tuebingen, Tuebingen, Germany

[2]Department of Paediatric Infectious Disease, Faculty of Medicine, Imperial College London, London, UK

[3]Pediatric Pharmacology and Pharmacogenetics, Hopital Universitaire Saint-Louis, Paris, France

[4]Clinical Investigation Center CIC1426, Hôpital Robert Debre, Paris, France

[5]Pharmacology, University of Paris, Paris, France

[6]Department of Respiratory Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

[7]Institute for Health Research, La Paz University Hospital, Madrid, Spain

[8]Pediatric Onco-Hematology Department, La Paz University Hospital, Madrid, Spain

[9]Faculty of Medicine, Autonomous University of Madrid, Madrid, Spain

[10]Department of Women's and Children's Health, University of Liverpool, UK

[11]NIHR Alder Hey Clinical Research Facility, Alder Hey Children's Hospital, Liverpool, UK

[12]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

[13]Department of Pharmacology and Toxicology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

[14]Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

[15]Departments of Clinical Pharmacology, and Biochemistry and Pharmacy, University of Tuebingen, Tuebingen, Germany

Correspondence
Matthias Schwab, Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Auerbachstrasse 112, 70376 Stuttgart, Germany.
Email: matthias.schwab@ikp-stuttgart.de

Funding information
Horizon 2020 Framework Programme, Grant/Award Numbers: 777389, Innovative Medicines Initiative 2 Joint Undertakin; Robert Bosch Stiftung

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 nontargeted 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,

Eva Neumann and Filippa Schreeck Contributed equally to this work.

including a subdivision into specific age groups as developmental changes clearly impact OMICs data. Second, compared to the adult population, the number of patients is limited as are the 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 (eg liquid biopsies) should be addressed to overcome these obstacles. The ultimate goal is to link OMICs technologies with innovative analysis tools, such as artificial intelligence at an early stage. The use of OMICs data based on a feasible approach will contribute to the identification complex phenotypes and subpopulations of patients to improve the development of medicines for children with potential economic advantages.

KEYWORDS
clinical trials, epigenomics, OMICS technology, paediatrics, pharmacogenomics

1 | INTRODUCTION

The interindividual variability in the 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 (eg, liver, kidney), age, weight and lifestyle as well as drug adherence.[1,2] Around 20% of adverse drug reactions (ADRs) are dose-independent, which cannot be explained from a drug's conventional pharmacology. These "off-target" drug effects may be explained by other factors, including pharmacogenomics (PGx) variation.[3,4]

With 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[5] 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.[3] 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 (absorption, distribution, metabolism, elimination) processes must be considered as well. This includes changes in 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 (eg, guanine nucleotide-binding proteins).[6] 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.[7] 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 intensively 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.[95]

2 | GENOMICS AND PGX

Genetic testing for variants underlying inherited diseases has been a fundamental part of the health system for 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 (eg, screening for trisomy 21). To achieve nationwide testing for a number of severe inherited diseases that are amenable to therapeutic strategies (eg, phenylketonuria), high-income developed countries and a steadily growing number of low- and middle-income countries have established 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, 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 NBS in addition to screening of nongenetic parameters (eg, 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 (eg, F508del). Most recently, a conferred additional benefit regarding efficacy and safety in children ≥12 years of age carrying the

TABLE 1 Summary of OMICs technologies

OMICs methods	Biomaterial	Methodology	Information	Application	Examples
Genomics	DNA germline and/or somatic	Targeted (eg, gene panel) and untargeted (eg, 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[3] Barry et al 2021[8] Caspar et al 2021[9] McDermott et al 2021[10] Nicoletti et al 2021[11] Franca et al 2020[12] Brown et al 2019[13] Drögemöller et al 2019[14] Relling et al 2019[15] Schaeffeler et al 2019[16] Wright et al 2019[17] Carter & McKone 2016[18] Lee et al 2016[19] Birdwell et al 2015[20] Diouf et al 2015[21] Fernandez et al 2014[22] Daly et al 2009[23]
Epigenomics	DNA/RNA, protein (tissue specific)	Targeted and untargeted (eg, EWAS, WGBS) methods	DNA modification, histone modification, miRNA expression	Identification of epigenomic variation related to disease and treatment response	Mendiola und LaSalle 2021[24] Bell et al 2019[25] Berdasco & Esteller 2019[26] Placek et al 2019[27] Felix et al 2018[28] Fisel et al 2018[29] Fisel et al 2016[30] Guo et al 2016[31] Neul et al 2016[32] Yiu & Li 2015[33] Kacevska et al 2012[34] Fraga et al 2005[35]
Transcriptomics	RNA (tissue-specific)	Targeted and untargeted (eg, RNA-Seq, microarray) methods	Individual gene expression profile	Identification of gene expression profiles related to disease and treatment response	Scott et al 2021[36] Umans et al 2021[37] Mulenga et al 2020[38] van Groen et al 2020[39] Montaldo et al 2019[40] Shiba et al 2019[41] Howell et al 2018[42] Kessler et al 2018[43] Rusch et al 2018[44] Wright et al 2018[45]

(Continues)

TABLE 1 (Continued)

OMICs methods	Biomaterial	Methodology	Information	Application	Examples
					Cummings et al 2017[46] Herberg et al 2016[47] Herberg et al 2013[48] Schröder et al 2013[49] Sadee et al 2011[50]
Proteomics	Protein (tissue-specific)	Targeted and untargeted methods (eg, LC-MS/MS)	Protein profiles	Protein biomarker development for disease and treatment	Dupree et al 2020[51] Kosteria et al 2018[52] Pereira-Fantini et al 2018[53] Wishart et al 2018[54] Cruz et al 2017[55] Froehlich et al 2014[56] López Villar et al 2014[57] Füzéry et al 2013[58] Saminathan et al 2010[59]
Metabolomics	Metabolites (endogenous/exogenous)	Targeted and untargeted methods (eg, LC-MS/MS, NMR)	Individual metabolite profiles	Identification of predictive metabolic biomarkers	Lammers et al 2021[60] Moor et al 2021[61] Beger et al 2020[62] Bessey et al 2020[63] Estrella et al 2020[64] Mordaunt et al 2020[65] Ellul et al 2019[66] Everett. 2019[67] Vries et al 2019[68] Wang et al 2019[69] Coene et al 2018[70] Shommu et al 2018[71] Turi et al 2018[72] de Vries et al 2018[73] Neerincx et al 2017[74] Trivedi et al 2017[75] Dessì et al 2014[76]
Microbiomics	Bacteria	DNA/RNA-Seq, bactieria culture	Microbiomic profile	Identification of disease and treatment-specific microbiomic patterns	Klünemann et al 2021[77] Cuthbertson et al 2020[78] Park et al 2020[79] Abdel-Aziz et al 2019[80] Dominguez-Bello et al 2019[81] Fessler et al 2019[82] Kang et al 2019[83] Peirce & Alviña 2019[84] Tuteja & Ferguson 2019[85] Gilbert et al 2018[86]

TABLE 1 (Continued)

OMICs methods	Biomaterial	Methodology	Information	Application	Examples
					Hughes et al 2018[87]
					Nishida et al 2018[88]
					Nusbaum et al 2018[89]
					Man et al 2017[90]
					Silbergeld 2017[91]
					Sim et al 2015[92]
					Kostic et al 2014[93]
					Haiser & Turnbaugh 2013[94]

Abbreviations: EWAS, epigenome-wide association study; GWAS, genome-wide association study; LC-MS/MS, liquid chromatography tandem mass spectrometry; miRNA, microRNA; NGS, next generation sequencing; NMR, nuclear magentic resonance; RNS-Seq, RNA sequencing; WGBS, whole-genome bisulfite sequencing.

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.[8] This example highlights the concept of PGx in children and the study of variations of germline DNA related to drug response.[18]

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.[96] Up to December 2020 the FDA listed 431 pharmacogenomic biomarkers in drug labelling, of which about 40% were related to oncology.[5] A total of 165 clinical annotation guidelines and 784 drug label annotations are currently available at the PharmGKB website.[97] 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.[98–103] As in adults, oncology is also pioneering in paediatric PGx and the example of treatment of childhood acute lymphoblastic leukemia demonstrates this enormous progress.[12] 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[15,16] and on vincristine-related neurotoxicity and variants in the gene encoding the centrosomal protein *CEP72*.[17,21]

Evidence for the benefit of preemptive and/or point-of-care PGx testing is growing.[104] The challenge for the implementation process of PGx into clinical practice is currently well addressed by various expert groups worldwide[105-107] but requires evidence-based data from clinical trials. As mentioned above, information from the CPIC, DPWG, 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.[108,109] 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 noncancer drugs, eg, atomoxetine and CYP2D6[13] as well as tacrolimus and CYP3A5.[20] The increased risk of aminoglycoside-induced hearing loss in association with variants of the *MT-RNR1* gene is another well-accepted example[10] since in young children hearing skills are not fully developed and the impact of ototoxicity is particularly high. Regarding the different PGx guidelines (CPIC, DPWG, CPNDS, RNPGx) some discordances exist, although the committees have similar methodologies of gudieline development.[3] For instance, cisplatin-induced hearing loss has been associated with an increased risk particularly in children carrying TPMT variants[14] and the FDA added PGx information to the cisplatin drug label.[5] However, so far only the CPNDS strongly recommends TPMT genotyping in children prior to starting a therapy with cisplatin.[19]

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.[133] In a very

TABLE 2 Currently available CPIC guidelines and specific paediatric recommendations

Drugs	Targets	Applicability to paediatric patients proposed	Specific paediatric recommendations
Abacavir[110]	HLA-B	Yes	No
Allopurinol[111]	HLA-B	Yes	No
Amikacin, gentamicin, kanamycin, paromomycin, plazomicin, streptomycin, tobramycin[10]	MT-RNR1	Yes	Yes
Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine[112]	CYP2C19, CYP2D6	Yes	No
atazanavir[113]	UGT1A1	Yes	No
atomoxetine[13]	CYP2D6	Yes	Yes
Azathioprine, mercaptopurine, thioguanine[15,114]	NUDT15, TPMT	Yes	Yes
Capecitabine, fluorouracil[115]	DPYD	Yes	No
Carbamazepine, oxcarbazepine[116]	HLA-A, HLA-B	Yes	No
Celecoxib, flurbiprofen, ibuprofen, lornoxicam, meloxicam, piroxicam, tenoxicam[117]	CYP2C9	Yes	No
Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline[118]	CYP2C19	Yes for CYP2D6, For CYP2C19 with caution	No
clopidogrel[119]	CYP2C19	Yes	No
Codeine, hydrocodone, tramadol[120]	CYP2D6, OPRM1, COMT	Yes	regulatory agencies (eg, FDA, EMA) advise against the use of codeine/tramadol in children <12 years and in children younger than 18 years of age after tonsillectomy and/or adenoidectomy. If codeine is used in some clinical settings/specific paediatric patient populations, careful CYP2D6 genotype-guided use of codeine should be considered
Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine[121]	CACNA1S, RYR1	Yes	There is less experience with MH susceptibility in children as compared with adults, but unpublished observations suggest that the risk of an MH reaction may be higher when an anesthetic is administered in childhood
Dexlansoprazole, lansoprazole, omeprazole, pantoprazole[122]	CYP2C19	Yes	Yes, only for paediatric patients >1 year
efavirenz[123]	CYP2B6	Yes	Yes, only for paediatric patients ≥40 kg body weight For children >3 years and <40 kg body weight TDM is recommended due to limited clinical data
Fosphenytoin, phenytoin[124]	CYP2C9, HLA-B	Yes	Yes, for HLA-B*15:02 For CYP2C9 only in combination with TDM
Ivacaftor[125]	CFTR	Yes	Yes, only for paediatric patients ≥6 years
Ondansetron, tropisetron[126]	CYP2D6	Yes	Because CYP2D6 catalytic activity in neonates (<1 month) depends strongly on developmental

TABLE 2 (Continued)

Drugs	Targets	Applicability to paediatric patients proposed	Specific paediatric recommendations
			aspects, the impact of CYP2D6 in this patient population might be different than adults or older children
Peginterferon alfa-2a, peginterferon alfa-2b, ribavirin[127]	IFNL3	No	No
Rasburicase[128]	G6PD	Yes	Yes
Simvastatin[129]	SLCO1B1	Yes	No
Tacrolimus[20]	CYP3A5	Yes	Yes
Tamoxifen[130]	CYP2D6	No	No
Voriconazole[131]	CYP2C19	Yes	Yes
Warfarin[132]	CYP2C9, CYP4F2, VKORC1	Yes	Yes, for children of European ancestry (CYP2C9 and VKORC1)

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; MH, malignant hyperthermia; TDM, therapeutic drug monitoring.

recent retrospective study, PGx testing of paediatric patients who were referred for pharmacogenetic testing was analysed. Almost half of these patients (48.7%) had a clinical diagnosis where the PGx results could help in selecting treatment options. In 15.0% of cases the PGx results could be used for dose adjustment of at least one currently prescribed drug. The two most common gene-drug diagnosis groups with matching clinical diagnosis and prescription were mood disorders and gastritis/esophagitis, and these are therefore considered promising targets for future studies in the area of PGx testing in children and adolescents.[134]

With advancing diagnostic technologies PGx testing has become faster, 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.[9] Targeted approaches like oligonucleotide microarrays or mass spectrometry-based assays (MALDI-TOF) to detect known single nucleotide polymorphisms (SNPs) and copy number variation are also very well established. Genome-wide assocation study (GWAS) can yield not only disease susceptibility genes, but also clinically relevant PGx information, as was nicely shown in the example of childhood leukemia.[12] One of the first landmark papers regarding GWAS PGx demonstrated that flucloxacillin-induced liver injury is associated with the *HLA-B*5701* allele.[23] 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,[11] and the higher incidence of hypersensitivity ($P = 7.5 \times 10,^5$ odds ratio 1.64) and anti-asparaginase antibodies ($P = 1.4 \times 10^5$, odds ratio 2.92) in children with asparaginase treatment for leukemia/lymphoma and HLA-DRB1*07:01.[22]

In this context, GWAS have proven useful to inform drug repurposing and to identify causal relationships between druggable exposures and complex diseases. For instance, thousands of variants that have been identified through GWAS related to clinically relevant phenotypes contribute to better understanding of the genes and pathways involved in disease pathophysiology. Mapping of genome-wide significant loci to drug targets with consequences for repurposed agents is promising for drug development and should be considered more intensively.[135]

What is widely accepted for inherited diseases, that early diagnosis and therapy yield 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,[136] 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.[137] Thus, the correlation between genotype and phenotype may still differ from adults since, for instance, post-transcriptional processes are also subject to developmental alterations and are 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 functionally relevant PGx variant. This phenomenon is well known in a figurative way in adult medicine and termed phenocopying. Here heterozygous patients result in a poor metabolizer phenotype due to inhibition of the remaining enzyme activity via drug-drug interaction.[138] Taken together, convincing examples are given that genomics and PGx research in paediatrics will promote individualized treatment and therefore should be strongly followed in clinical trial activities during the drug development process.[139] Nevertheless, it has been shown that genetic information, even if next-generation sequencing strategies have been applied, is limited to explain the interindividual variability of hepatic expression and function of ADME targets such as drug metabolizing enzymes or transporters with consequences for drug response.[140–142] Therefore, other underlying mechanisms need to be identified through consideration of innovative approaches.

3 | EPIGENOMICS

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 microRNA expression.[26] Extensive DNA methylation plasticity is known to occur during embryogenesis. This is crucial for the 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 responsive nature of epigenetics.[35] In oncology specific epigenetic profiles are associated with cancer development, thereby demonstrating the relationship between the epigenome and disease.[143] 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,[27,28] nicely shown by the example of Prader-Willi syndrome and transient neonatal diabetes mellitus.[24]

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.[30] 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.[33]

The impact of ageing in adults on DNA methylation is well addressed, with consequences on drug targeting and treatment strategies.[25] Different studies and meta-analyses comparing paediatric and adult data demonstrate qualitative and quantitative differences in DNA methylation patterns occurring over a lifetime. Moreover, there is increasing evidence that epigenetic regulation via DNA methylation has a major impact on the expression of pharmacogenes (eg, ADME genes), which promotes research activity known as pharmacoepigenomics.[30] 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.[34] Comparable results were found for CYP2W1 expression indicating silencing of expression of CYP2W1 by epigenetic regulation in healthy adult tissues compared to the foetal gut.[31] Regarding drug transport, hyper- and hypomethylation of efflux and uptake transporter proteins from the ABC (eg, ABCB1, ABCG2) and SLC transporter families (eg, OCT1, MCTs) are well described with consequences for pharmacokinetics and pharmacodynamics.[29,30,32]

To this end, pharmacoepigenomics needs to be addressed more systematically in paediatric drug research, including clinical trial activities. Of note, epigenetic analyses are tissue-specific and this may limit the feasibility of research activites in children where the availability of tissue biopsies is extremly limited. However, for example, the noninvasive approach of DNA methylation analysis in body fluids using cell-free circulating DNA in blood is promising, particular for cancer drugs, but warrants futher investigation.

4 | TRANSCRIPTOMICS

In addition to DNA sequencing and epigentic studies, transcriptomics adds 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,[144,145] as are feedback mechanisms of transcriptomic products on the epigenome.[146] Similar to epigenomics, transcriptome analyses are cell/tissue-specific.[147]

In general post-transcriptional modifications are fundamental for the functionality of the cytochrome P450 superfamily enzymes, which are essential for the metabolism of xenobiotics.[148] Types of post-transcriptional 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 by the *CYP3A5*1* variant.[50] 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.[39]

The majority of trait-associated SNPs are not located in protein coding regions and are likely to act via modification of gene expression. Expression quantitative trait loci (eQTL) studies are going beyond univariate SNP-transcript associations and differentiate between *cis* (ie, located within the transcribed gene region) and *trans* (ie, distant) eQTLs to uncover biological pathways and polygenetic effects of expression regulation, including the enrichment of colocalized functional elements. Several eQTL-studies in different adult tissues (eg, human liver) have been published,[49] but with the limitation of small sample sizes. Novel technologies to cover more diverse, disease-relevant cell types have been recently suggested.[37] Whilst hybridization-based microarrays for transcriptional profiling have been used to provide information on diagnosis, prognosis and optimal treatment,[149] current approaches combine RNA-sequencing (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,[41,44] transcriptomic profiles of diseased tissue offer a window into a wide range of paediatric conditions, including inflammatory bowel disease[42] and juvenile idiopathic arthritis.[43] RNA-Seq approaches can complement genomic sequencing to yield improved genetic diagnoses in Mendelian disease with consequences for drug therapy and drug development.[46] 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.[150] In infectious diseases, blood signatures may be pathogen-specific[48] or class-specific,[47] and this enables understanding of disease progression, for instance in tuberculosis.[38] The utility of transcriptomics for biological understanding and diagnosis extends beyond infectious problems to inflammatory conditions such as Kawasaki disease[45] and non-inflammatory conditions including neonatal encephalopathy.[40] 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 growth/differentiation factor 5.[36] We therefore encourage paediatric clinical trials to incorporate sampling for transcriptomic studies, particularly in combination with other analyses such as genomic approaches.

5 | PROTEOMICS

Epigenomics and transcriptomics are crucial for better understanding of phenotype-genotype correlations. In addition, protein data provide 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, regulation via miRNAs, proteasomal degradation and post-translational modifications. Proteomics covers exhaustive analytical methods including mass-spectrometry tecniques such liquid chromatography tandem mass spectrometry and matrix assisted laser desorption/ionization tandem time-of-flight mass spectrometry.[151] 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.[51] A specific area in drug research is pharmacoproteomics, with examples such as carboplatin and paclitaxel resistance in ovarian cancer.[55] Promising results of a combination of pharmacoproteomics with PGx have been reported for warfarin[59] and recently DrugBank,[152] 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.[54]

Paediatric proteomic research has also been widely conducted in some areas, including acute lymphablastic leukemia,[57] type 1 diabetes[52] and ventilator-induced lung injury.[53] 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.[56] Although a huge number of potentially relevant protein biomarkers is identified each year in drug research, only a small number reach validation and approval by the FDA.[58] Although a diverse variety of databases 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.

6 | METABOLOMICS

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 (eg, 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.[153] Here again developmental aspects resulting in functional consequences particularly related to paediatric medicines are included.[154] 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 (elevated concentration of phenylalanine and galactose in blood) that is based on metabolomics.[65] Novel mass spectrometry technologies improved NBS significantly,

measuring a huge variety of endogenous compounds in a less time- and cost-consuming manner.[63] Moreover, innovations such as next-generation metabolic screening as an untargeted metabolomics approach appear to be promising.[70] Beyond NBS, metabolomics is well established for diagnosis of other diseases in childhood. One major advantage is that noninvasive biosamples can be used, such as urine,[155] saliva and blood. Methodologies such as dried blood spots are being introduced to overcome the limited amount of biomaterial, particularly in the preterm and newborn settings.

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 (eg, childhood asthma[72] or infection[69]) but also to drug-related metabolic alteration.[66,75] Another promising noninvasive method in paediatric metabolomics is breathomics, with specific focus on exhaled volatile organic compounds (VOC) in paediatric asthma.[74] VOCs in exhaled breath come from the lungs, but also via the lungs from the general circulation, and various techniques (eg, electronic nose analysis, mass spectrometry) can be used for analysis. Notably, breathomics allows the detection of bacterial and/or viral infections,[60] the amount of inflammatory cells in blood,[73] different diagnosis of respiratory diseases[61] and response to medication.[68]

The application of metabolomics and better understanding of endogenous metabolism in the nutrition of neonates has been nicely shown by the work of Dessi et al.[76] A further interesting paediatric example is the application of metabolomics to differentiate between children with and without typical symptoms of gastrointestinal 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 nonappendicitis-related abdominal pain, and perforated and non-perforated appendicitis.[71]

Thus, clinical trial monitoring not only involves monitoring of drug effects, but also diet, food by-products, additional drug use, herbal supplements, individual ADME phenotypes, etc. Implementation of pharmacometabolomics and particularly pharmacometabolomics-informed PGx in drug devlopment is increasing. Several excellent reviews[62,67,156] have been published demonstrating that metabolomic profiles are associated with variable pharmacological response followed by the identification of subphenotypes 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 overall.

7 | MICROBIOMICS

The move to recognize the microbiome as a human organ has helped increase awareness of microbiomic research in the scientific community.[157] 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 (eg, plants and animal species). However, there is now convincing data demonstrating the microbiome's impact on various diseases, such as gastrointestinal (eg, inflammatory bowel diseases[88,93] or necrotizing enterocolitis[92]) and hepatic diseases (eg, hepatic steatosis),[88] several types of cancer[82] and asthma[80] as well as mental illnesses such as major depressive disorder.[84] A strong interaction of the microbiome with the immune, endocrine, metabolic and nervous systems is well accepted.[86] Thus, for example, microbes colonize not only the gut but are also detected in the respiratory and genitourinary tract and tissues without disease-causing effects.[91]

The microbiome underlies developmental processes as well, which requires age-specific research activites. Moreover, the impact of drug treatment on the microbiome with clinical consequences in later in life has nicely been shown for Caesarean section and early antibiotic exposure interfering with the natural microbiome development and obesity risk.[81] Other examples are reported are the association with progress for respiratory diseases[78,90] and most strikingly the contribution of the microbiome in autism spectrum disorder.[87]

The concept of the therapeutic potential of the microbiome is emerging. Here, the first evidence is reported in children with inflammatory bowel diseases[89] and autism spectrum disorders[83] and the use of probiotics as well as 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.[79] The gut microbiome may also have an impact on the first-pass metabolism of drugs. This has been shown for more than 50 drugs metabolized by the gut microbiome, including drugs that are used in daily practice, such as omeprazole.[94] Moreover, the absorption (eg, digoxin), distribution (eg, sulfasalazine) and elimination (eg, irinotecan) of drugs[85] 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 for decades.[158] A 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 contributes significantly to drug availability and bacterial metabolism with consequences for pharmacokinetics, ADR and drug response.[77] Thus, the microbiome is probably the most innovative OMICs field, with enormous potential not only for adults but also for children, and consequences for future therapeutic options.

8 | CONSEQUENCES FOR PAEDIATRIC CLINICAL TRIALS

Based on data from adults there is increasing evidence that various OMICs technologies contribute substantially to better understanding of drug-related events, including 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 have changed traditional clinical drug development of phases 1 to 3.[159] Between 2015 and 2019 more than half of EU and US approvals were supported by biomarker data during at least one of the development stages.[159] Notably, the ICH Guideline E16 describing the context, structure and format of qualification submissions for clinical and non-clinical genomic biomarkers related to drug development[160] is applicable also to other types of biomarkers, thereby increasing the acceptance of biomarkers in the global drug development process.[161]

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 children for the conservation and reuse 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 noninvasive specimen for proteomics and metabolomics analyses are feasible to obtain. Besides serum, saliva can be used for molecular analyses. Residual 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[162] reported that noninvasive 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.[163] Moreover, Estrella et al successfully used NBS blood spots for further analysis investigating biomarkers for the disease pathophysiology of diabetes type 1.[64] 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 the combination of precise phenotypic data for comprehensive data analysis and further research activities. Necessary financial resources should be provided either through partnerships with the pharmaceutical industry or through public third-party funding (eg, EU projects).

Innovative IT-based modelling tools, such as physiologically-based pharmacokinetic (PBPK) modelling and system medicine approaches, are crucial for an innovative future pediatric drug

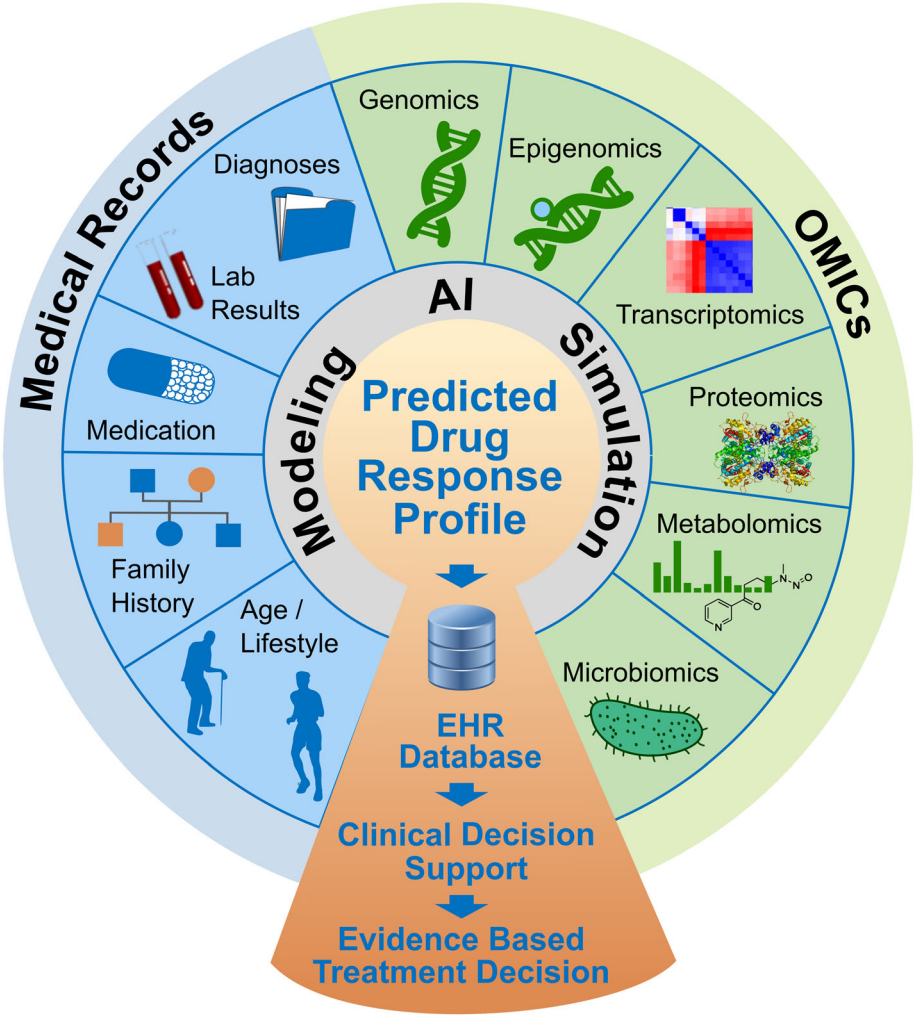

FIGURE 1 Information flow and application of OMICs technologies to personalized medicine in children. The integration of clinical data and data from genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics based on prior biological knowledge enables the opportunity to develop specific classifiers for personalized medicine. A central element of this workflow is the systematic computational network analysis comprising various approaches

development process. PBPK enables the integration of various OMICs data based on information from drug trials and/or literature reviews, 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 subsequent 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.[164–166] Importantly, PGx information, for instance with an impact on drug-related ADME processes, can be included as well.[167] A digitizing software solution as a tool for PBPK modelling to gather data from graphical representations with excellent accuracy and precision has also been established.[168] Novel concepts of a more holistic view based on multilayer network theory and artificial intelligence may also ensure better integration of multi-OMICs data.[169]

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 in contrast to the collection of real-world data will contribute to the improvement and even optimization of the drug development process with benefits for research and development productivity, including economic aspects, as has been demonstrated for the adult situation.[170,159]

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

ACKNOWLEDGEMENTS

The conect4children (c4c) project has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. E.N., E.S., F.S. and M.S. are supported by Robert Bosch Stiftung, Stuttgart, Germany.

COMPETING INTERESTS

E.N., no conflicts of interest to declare. F.S., no conflicts of interest to declare. J.H., no conflicts of interest to declare. E.J.A., no conflicts of interest to declare. A.-H.M.-vanderZ. has received research grants outside the submitted work from GSK, Boehringer Íngelheim and Vertex, is the PI of a P4O2 (Precision Medicine for more Oxygen) public private partnership sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (Boehringer Ingelheim, Breathomix, Fluidda, Ortec Logiqcare, Philips, Quantib-U, Smartfish, SODAQ, Thirona, TopMD and Novartis), and has served in advisory boards for AstraZeneca, GSK and Boehringer Ingelheim with money paid to her institution. Antonio Pérez-Martínez, no conflicts of interest to declare. D.H., no conflicts of interest to declare. E.S., no conflicts of interest to declare. A.R., no conflicts of interest to declare. S.deW. has received research grants outside the submitted work from Health Holland, in a public private partnership with UCB Pharma and served on advisory boards from AM Pharma, Novartis, Khondrion, and is also co-chair of the IMI2 C4C strategic feasibility expert work package and director of the secretariat. M.S. has received research grants outside the submitted work from Green Cross WellBeing Co. Ltd, from Gilead Sciences Inc., from Agena Bioscience GmbH, CED Service GmbH, and from the Robert Bosch GmbH, and has received honoraria for oral presentations at academically organized congresses and meetings.

CONFIDENTIALITY

Use of the information in this manuscript for commercial, non-commercial, research or purposes other than peer review is not permitted prior to publication without the expressed written permission of the author.

DISCLAIMER

This publication reflects the author's view and neither IMI nor the European Union, EFPIA or any associated partners are responsible for any use that may be made of the information contained therein.

CONTRIBUTORS

E.N. and M.S.: conducted research, manuscript writing. F.S., J.H., E.J.A., A.H.M.vdZ., A.P.-M., D.B.H., E.S., A.R., S.deW.: supervised research, manuscript writing and editing.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Filippa Schreeck https://orcid.org/0000-0002-9343-6684
Jethro Herberg https://orcid.org/0000-0001-6941-6491
Evelyne Jacqz Aigrain https://orcid.org/0000-0002-4285-7067
Matthias Schwab https://orcid.org/0000-0002-9984-075X

REFERENCES

1. Lonergan M, Senn SJ, McNamee C, et al. Defining drug response for stratified medicine. *Drug Discov Today*. 2017;22(1):173-179. doi:10.1016/j.drudis.2016.10.016
2. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther*. 2013;138(1):103-141. doi:10.1016/j.pharmthera.2012.12.007
3. Abdullah-Koolmees H, van Keulen AM, Nijenhuis M, Deneer VHM. Pharmacogenetics Guidelines: Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines. *Front Pharmacol*. 2021;11:595219. doi:10.3389/fphar.2020.595219
4. Osanlou O, Pirmohamed M, Daly AK. Chapter Seven – Pharmacogenetics of Adverse Drug Reactions. In: Brøsen K, Damkier P, eds. *Advances in Pharmacology: Pharmacogenetics*. Vol. 83 Academic Press; 2018:155-190.
5. Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. 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. Updated August 18, 2020. Accessed December 31, 2020.
6. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Steven LJ, Kauffman RE. Developmental pharmacology — Drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;1157-1167.
7. Burckart GJ, Seo S, Pawlyk AC, et al. Scientific and regulatory considerations for an ontogeny knowledge base for pediatric clinical pharmacology. *Clin Pharmacol Ther*. 2020;107(4):707-709. doi:10.1002/cpt.1763
8. Barry PJ, Mall MA, Álvarez A, et al. Triple therapy for cystic fibrosis Phe508del-gating and -residual function genotypes. *N Engl J Med*. 2021;385(9):815-825. doi:10.1056/NEJMoa2100665
9. Caspar SM, Schneider T, Stoll P, Meienberg J, Matyas G. Potential of whole-genome sequencing-based pharmacogenetic profiling. *Pharmacogenomics*. 2021;22(3):177-190. doi:10.2217/pgs-2020-0155
10. McDermott JH, Wolf J, Hoshitsuki K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for the Use of Aminoglycosides Based on MT-RNR1 Genotype. *Clin Pharmacol Ther*. 2022;111:366-372. doi:10.1002/cpt.2309
11. Nicoletti P, Carr DF, Barrett S, et al. Beta-lactam-induced immediate hypersensitivity reactions: A genome-wide association study of a deeply phenotyped cohort. *J Allergy Clin Immunol*. 2021;147(5):1830-1837. doi:10.1016/j.jaci.2020.10.004
12. Franca R, Zudeh G, Lucafò M, Rabusin M, Decorti G, Stocco G. Genome wide association studies for treatment-related adverse effects of pediatric acute lymphoblastic leukemia. *Wiley Interdiscip Rev Syst Biol Med*. 2020;13(3):e1509. doi:10.1002/wsbm.1509
13. Brown JT, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP) 2D6 Genotype and Atomoxetine Therapy. *Clin Pharmacol Ther*. 2019;106(1):94-102. doi:10.1002/cpt.1409
14. Drögemöller BI, Wright GEB, Lo C, et al. Pharmacogenomics of cisplatin-induced ototoxicity: Successes, shortcomings, and future avenues of research. *Clin Pharmacol Ther*. 2019;106(2):350-359. doi:10.1002/cpt.1483
15. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. *Clin Pharmacol Ther*. 2019;105(5):1095-1105. doi:10.1002/cpt.1304
16. Schaeffeler E, Jaeger SU, Klumpp V, et al. Impact of NUDT15 genetics on severe thiopurine-related hematotoxicity in patients with European ancestry. *Genet Med*. 2019;21(9):2145-2150. doi:10.1038/s41436-019-0448-7
17. Wright GEB, Amstutz U, Drögemöller BI, et al. Pharmacogenomics of vincristine-induced peripheral neuropathy implicates pharmacokinetic and inherited neuropathy genes. *Clin Pharmacol Ther*. 2019;105(2):402-410. doi:10.1002/cpt.1179
18. Carter SC, McKone EF. Pharmacogenetics of cystic fibrosis treatment. *Pharmacogenomics*. 2016;17(13):1453-1463. doi:10.2217/pgs.16.25
19. Lee JW, Pussegoda K, Rassekh SR, et al. Clinical practice recommendations for the management and prevention of cisplatin-induced hearing loss using pharmacogenetic markers. *Ther Drug Monit*. 2016;38(4):423-431. doi:10.1097/FTD.0000000000000298
20. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. *Clin Pharmacol Ther*. 2015;98(1):19-24. doi:10.1002/cpt.113
21. Diouf B, Crews KR, Lew G, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. *Jama*. 2015;313(8):815-823. doi:10.1001/jama.2015.0894
22. Fernandez CA, Smith C, Yang W, et al. HLA-DRB1*07: 01 is associated with a higher risk of asparaginase allergies. *Blood*. 2014;124(8):1266-1276. doi:10.1182/blood-2014-03-563742
23. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet*. 2009;41(7):816-819. doi:10.1038/ng.379
24. Mendiola AJP, LaSalle JM. Epigenetics in Prader-Willi syndrome. *Front Genet*. 2021;12:624581. doi:10.3389/fgene.2021.624581
25. Bell CG, Lowe R, Adams PD, et al. DNA methylation aging clocks: challenges and recommendations. *Genome Biol*. 2019;20(1):249. doi:10.1186/s13059-019-1824-y
26. Berdasco M, Esteller M. Clinical epigenetics: seizing opportunities for translation. *Nat Rev Genet*. 2019;20(2):109-127. doi:10.1038/s41576-018-0074-2
27. Placek K, Schultze JL, Aschenbrenner AC. Epigenetic reprogramming of immune cells in injury, repair, and resolution. *J Clin Invest*. 2019;129(8):2994-3005. doi:10.1172/JCI124619
28. Felix JF, Joubert BR, Baccarelli AA, et al. Cohort Profile: Pregnancy And Childhood Epigenetics (PACE) Consortium. *Int J Epidemiol*. 2018;47(1):22-23u. doi:10.1093/ije/dyx190.
29. Fisel P, Schaeffeler E, Schwab M. Clinical and functional relevance of the monocarboxylate transporter family in disease pathophysiology and drug therapy. *Clin Transl Sci*. 2018;11(4):352-364. doi:10.1111/cts.12551
30. Fisel P, Schaeffeler E, Schwab M. DNA methylation of ADME genes. *Clin Pharmacol Ther*. 2016;99(5):512-527. doi:10.1002/cpt.343
31. Guo J, Johansson I, Mkrtchian S, Ingelman-Sundberg M. The CYP2W1 enzyme: regulation, properties and activation of prodrugs. *Drug Metab Rev*. 2016;48(3):369-378. doi:10.1080/03602532.2016.1188939
32. Neul C, Schaeffeler E, Sparreboom A, Laufer S, Schwab M, Nies AT. Impact of membrane drug transporters on resistance to small-molecule tyrosine kinase inhibitors. *Trends Pharmacol Sci*. 2016;37(11):904-932. doi:10.1016/j.tips.2016.08.003
33. Yiu TT, Li W. Pediatric cancer epigenome and the influence of folate. *Epigenomics*. 2015;7(6):961-973. doi:10.2217/epi.15.42
34. Kacevska M, Ivanov M, Wyss A, et al. DNA methylation dynamics in the hepatic CYP3A4 gene promoter. *Biochimie*. 2012;94(11):2338-2344. doi:10.1016/j.biochi.2012.07.013
35. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA*. 2005;102(30):10604-10609. doi:10.1073/pnas.0500398102
36. Scott EN, Wright GEB, Drögemöller BI, et al. Transcriptome-wide association study uncovers the role of essential genes in

anthracycline-induced cardiotoxicity. *NPJ Genom Med*. 2021;6(1):35. doi:10.1038/s41525-021-00199-4
37. Umans BD, Battle A, Gilad Y. Where are the disease-associated eQTLs? *Trends Genet*. 2021;37:109-124. doi:10.1016/j.tig.2020.08.009
38. Mulenga H, Zauchenberger C-Z, Bunyasi EW, et al. Performance of diagnostic and predictive host blood transcriptomic signatures for tuberculosis disease: A systematic review and meta-analysis. *PLoS ONE*. 2020;15(8):e0237574. doi:10.1371/journal.pone.0237574
39. van Groen BD, Bi C, Gaedigk R, et al. Alternative splicing of the SLCO1B1 gene: An exploratory analysis of isoform diversity in pediatric liver. *Clin Transl Sci*. 2020;13(3):509-519. doi:10.1111/cts.12733
40. Montaldo P, Kaforou M, Pollara G, et al. Whole blood gene expression reveals specific transcriptome changes in neonatal encephalopathy. *Neonatology*. 2019;115(1):68-76. doi:10.1159/000492420
41. Shiba N, Yoshida K, Hara Y, et al. Transcriptome analysis offers a comprehensive illustration of the genetic background of pediatric acute myeloid leukemia. *Blood Adv*. 2019;3(20):3157-3169. doi:10.1182/bloodadvances.2019000404
42. Howell KJ, Kraiczy J, Nayak KM, et al. DNA methylation and transcription patterns in intestinal epithelial cells from pediatric patients with inflammatory bowel diseases differentiate disease subtypes and associate with outcome. *Gastroenterology*. 2018;154(3):585-598. doi:10.1053/j.gastro.2017.10.007
43. Kessler H, Jiang K, Jarvis JN. Using chromatin architecture to understand the genetics and transcriptomics of juvenile idiopathic arthritis. *Front Immunol*. 2018;9:2964. doi:10.3389/fimmu.2018.02964
44. Rusch M, Nakitandwe J, Shurtleff S, et al. Clinical cancer genomic profiling by three-platform sequencing of whole genome, whole exome and transcriptome. *Nat Commun*. 2018;9(1):3962. doi:10.1038/s41467-018-06485-7
45. Wright VJ, Herberg JA, Kaforou M, et al. Diagnosis of Kawasaki disease using a minimal whole-blood gene expression signature. *JAMA Pediatr*. 2018;172(10):e182293. doi:10.1001/jamapediatrics.2018.2293
46. Cummings BB, Marshall JL, Tukiainen T, et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. *Sci Transl Med*. 2017;9(386): doi:10.1126/scitranslmed.aal5209
47. Herberg JA, Kaforou M, Wright VJ, et al. Diagnostic test accuracy of a 2-transcript host RNA signature for discriminating bacterial vs viral infection in febrile children. *Jama*. 2016;316(8):835-845. doi:10.1001/jama.2016.11236
48. Herberg JA, Kaforou M, Gormley S, et al. Transcriptomic profiling in childhood H1N1/09 influenza reveals reduced expression of protein synthesis genes. *J Infect Dis*. 2013;208(10):1664-1668. doi:10.1093/infdis/jit348
49. Schröder A, Klein K, Winter S, et al. Genomics of ADME gene expression: mapping expression quantitative trait loci relevant for absorption, distribution, metabolism and excretion of drugs in human liver. *Pharmacogenomics J*. 2013;13(1):12-20. doi:10.1038/tpj.2011.44
50. Sadee W, Wang D, Papp AC, et al. Pharmacogenomics of the RNA world: structural RNA polymorphisms in drug therapy. *Clin Pharmacol Ther*. 2011;89(3):355-365. doi:10.1038/clpt.2010.314
51. Dupree EJ, Jayathirtha M, Yorkey H, Mihasan M, Petre BA, Darie CC. A critical review of bottom-up proteomics: The good, the bad, and the future of this field. *Proteomes*. 2020;8(3):14. doi:10.3390/proteomes8030014
52. Kosteria I, Kanaka-Gantenbein C, Anagnostopoulos AK, Chrousos GP, Tsangaris GT. Pediatric endocrine and metabolic diseases and proteomics. *J Proteomics*. 2018;188:46-58. doi:10.1016/j.jprot.2018.03.011
53. Pereira-Fantini PM, Byars SG, McCall KE, et al. Plasma proteomics reveals gestational age-specific responses to mechanical ventilation and identifies the mechanistic pathways that initiate preterm lung injury. *Sci Rep*. 2018;8(1):12616. doi:10.1038/s41598-018-30868-x
54. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res*. 2018;46(D1):D1074-D1082. doi:10.1093/nar/gkx1037
55. Cruz IN, Coley HM, Kramer HB, et al. Proteomics analysis of ovarian cancer cell lines and tissues reveals drug resistance-associated proteins. *Cancer Genomics Proteomics*. 2017;14(1):35-51. doi:10.21873/cgp.20017
56. Froehlich JW, Vaezzadeh AR, Kirchner M, et al. An in-depth comparison of the male pediatric and adult urinary proteomes. *Biochim Biophys Acta*. 2014;1844(5):1044-1050. doi:10.1016/j.bbapap.2013.05.008
57. López Villar E, Wu D, Cho WC, Madero L, Wang X. Proteomics-based discovery of biomarkers for paediatric acute lymphoblastic leukaemia: challenges and opportunities. *J Cell Mol Med*. 2014;18(7):1239-1246. doi:10.1111/jcmm.12319
58. Füzéry AK, Levin J, Chan MM, Chan DW. Translation of proteomic biomarkers into FDA approved cancer diagnostics: Issues and challenges. *Clin Proteomics*. 2013;10(1):13. doi:10.1186/1559-0275-10-13
59. Saminathan R, Bai J, Sadrolodabaee L, et al. VKORC1 pharmacogenetics and pharmacoproteomics in patients on warfarin anticoagulant therapy: transthyretin precursor as a potential biomarker. *PLoS ONE*. 2010;5(12):e15064. doi:10.1371/journal.pone.0015064
60. Lammers A, Brinkman P, Te Nijenhuis L, et al. Increased day-to-day fluctuations in exhaled breath profiles aftera rhinovirus challenge in asthma. *Allergy*. 2021;76(8):2488-2499. doi:10.1111/all.14811
61. Moor CC, Oppenheimer JC, Nakshbandi G, et al. Exhaled breath analysis by use of eNose technology: a novel diagnostic tool for interstitial lung disease. *Eur Respir J*. 2021;57(1):2002042. doi:10.1183/13993003.02042-2020
62. Beger RD, Schmidt MA, Kaddurah-Daouk R. Current concepts in pharmacometabolomics, biomarker discovery, and precision medicine. *Metabolites*. 2020;10(4):129. doi:10.3390/metabo10040129
63. Bessey A, Chilcott J, Pandor A, Paisley S. The cost-effectiveness of expanding the UK newborn bloodspot screening programme to include five additional inborn errors of metabolism. *Int J Neonatal Screen*. 2020;6(4):93. doi:10.3390/ijns6040093
64. Estrella JFGL, Immanuel J, Wiley V, Simmons D. Newborn screening samples for diabetes research: An underused resource. *Cells*. 2020;9(10):2299. doi:10.3390/cells9102299
65. Mordaunt D, Cox D, Fuller M. Metabolomics to improve the diagnostic efficiency of inborn errors of metabolism. *Int J Mol Sci*. 2020;21(4):1195. doi:10.3390/ijms21041195
66. Ellul S, Wake M, Clifford SA, et al. Metabolomics: population epidemiology and concordance in Australian children aged 11-12 years and their parents. *BMJ Open*. 2019;9(Suppl 3):106-117. doi:10.1136/bmjopen-2017-020900
67. Everett JR. Pharmacometabonomics: The prediction of drug effects using metabolic profiling. In: Barrett JE, Page CP, Michel MC, eds. *Concepts and Principles of Pharmacology: 100 Years of the Handbook of Experimental Pharmacology*. Cham: Springer International Publishing; 2019:263-299.
68. de Vries R, Muller M, van der Noort V, et al. Prediction of response to anti-PD-1 therapy in patients with non-small-cell lung cancer by electronic nose analysis of exhaled breath. *Ann Oncol*. 2019;30(10):1660-1666. doi:10.1093/annonc/mdz279
69. Wang X, Nijman R, Camuzeaux S, et al. Plasma lipid profiles discriminate bacterial from viral infection in febrile children. *Sci Rep*. 2019;9(1):17714. doi:10.1038/s41598-019-53721-1
70. Coene KLM, Kluijtmans LAJ, van der Heeft E, et al. Next-generation metabolic screening: targeted and untargeted metabolomics for the

diagnosis of inborn errors of metabolism in individual patients. *J Inherit Metab Dis*. 2018;41(3):337-353. doi:10.1007/s10545-017-0131-6

71. Shommu NS, Jenne CN, Blackwood J, et al. The use of metabolomics and inflammatory mediator profiling provides a novel approach to identifying pediatric appendicitis in the emergency department. *Sci Rep*. 2018;8(1):4083. doi:10.1038/s41598-018-22338-1
72. Turi KN, Romick-Rosendale L, Ryckman KK, Hartert TV. A review of metabolomics approaches and their application in identifying causal pathways of childhood asthma. *J Allergy Clin Immunol*. 2018;141(4):1191-1201. doi:10.1016/j.jaci.2017.04.021
73. de Vries R, Dagelet YWF, Spoor P, et al. Clinical and inflammatory phenotyping by breathomics in chronic airway diseases irrespective of the diagnostic label. *Eur Respir J*. 2018;51(1):1701817. doi:10.1183/13993003.01817-2017
74. Neerincx AH, Vijverberg SJH, Bos LDJ, et al. Breathomics from exhaled volatile organic compounds in pediatric asthma. *Pediatr Pulmonol*. 2017;52(12):1616-1627. doi:10.1002/ppul.23785
75. Trivedi DK, Hollywood KA, Goodacre R. Metabolomics for the masses: The future of metabolomics in a personalized world. *New Horiz Transl Med*. 2017;3(6):294-305. doi:10.1016/j.nhtm.2017.06.001
76. Dessì A, Cesare Marincola F, Masili A, Gazzolo D, Fanos V. Clinical metabolomics and nutrition: the new frontier in neonatology and pediatrics. *Biomed Res Int*. 2014;2014:981219. doi:10.1155/2014/981219
77. Klünemann M, Andrejev S, Blasche S, et al. Bioaccumulation of therapeutic drugs by human gut bacteria. *Nature*. 2021;597(7877):533-538. doi:10.1038/s41586-021-03891-8
78. Cuthbertson L, Walker AW, Oliver AE, et al. Lung function and microbiota diversity in cystic fibrosis. *Microbiome*. 2020;8(1):45. doi:10.1186/s40168-020-00810-3
79. Park I-H, Lee JS, Park J-H, et al. Comparison of the human microbiome in adults and children with chronic rhinosinusitis. *PLoS ONE*. 2020;15(12):e0242770. doi:10.1371/journal.pone.0242770
80. Abdel-Aziz MI, Vijverberg SJH, Neerincx AH, Kraneveld AD, Maitland-van der Zee AH. The crosstalk between microbiome and asthma: Exploring associations and challenges. *Clin Exp Allergy*. 2019;49(8):1067-1086. doi:10.1111/cea.13444
81. Dominguez-Bello MG, Godoy-Vitorino F, Knight R, Blaser MJ. Role of the microbiome in human development. *Gut*. 2019;68(6):1108-1114. doi:10.1136/gutjnl-2018-317503
82. Fessler J, Matson V, Gajewski TF. Exploring the emerging role of the microbiome in cancer immunotherapy. *J Immunother Cancer*. 2019;7(1):108. doi:10.1186/s40425-019-0574-4
83. Kang D-W, Adams JB, Coleman DM, et al. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. *Sci Rep*. 2019;9(1):5821. doi:10.1038/s41598-019-42183-0
84. Peirce JM, Alviña K. The role of inflammation and the gut microbiome in depression and anxiety. *J Neurosci Res*. 2019;97(10):1223-1241. doi:10.1002/jnr.24476
85. Tuteja S, Ferguson JF. Gut microbiome and response to cardiovascular drugs. *Circ Genom Precis Med*. 2019;12(9):421-429. doi:10.1161/CIRCGEN.119.002314
86. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. *Nat Med*. 2018;24(4):392-400. doi:10.1038/nm.4517
87. Hughes HK, Rose D, Ashwood P. The gut microbiota and dysbiosis in autism spectrum disorders. *Curr Neurol Neurosci Rep*. 2018;18(11):81. doi:10.1007/s11910-018-0887-6
88. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin J Gastroenterol*. 2018;11(1):1-10. doi:10.1007/s12328-017-0813-5
89. Nusbaum DJ, Sun F, Ren J, et al. Gut microbial and metabolomic profiles after fecal microbiota transplantation in pediatric ulcerative colitis patients. *FEMS Microbiol Ecol*. 2018;94(9): doi:10.1093/femsec/fiy133
90. Man WH, Steenhuijsen Piters WAA, de Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol*. 2017;15(5):259-270. doi:10.1038/nrmicro.2017.14
91. Silbergeld EK. The microbiome. *Toxicol Pathol*. 2017;45(1):190-194. doi:10.1177/0192623316672073
92. Sim K, Shaw AG, Randell P, et al. Dysbiosis anticipating necrotizing enterocolitis in very premature infants. *Clin Infect Dis*. 2015;60(3):389-397. doi:10.1093/cid/ciu822
93. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology*. 2014;146(6):1489-1499. doi:10.1053/j.gastro.2014.02.009
94. Haiser HJ, Turnbaugh PJ. Developing a metagenomic view of xenobiotic metabolism. *Pharmacol Res*. 2013;69(1):21-31. doi:10.1016/j.phrs.2012.07.009
95. IMI. conect4children. https://www.imi.europa.eu/projects-results/project-factsheets/c4c. Accessed April 26, 2021.
96. Green D. Ontogeny and the application of pharmacogenomics to pediatric drug development. *J Clin Pharmacol*. 2019;59(S1):S82-S86. doi:10.1002/jcph.1488
97. PharmGKB. Pharmakogenomic Knowledge Base. https://www.pharmgkb.org/. Accessed April 14, 2021.
98. Gregornik D, Salyakina D, Brown M, Roiko S, Ramos K. Pediatric pharmacogenomics: challenges and opportunities: on behalf of the Sanford Children's Genomic Medicine Consortium. *Pharmacogenomics J*. 2021;21(1):8-19. doi:10.1038/s41397-020-00181-w
99. Stevens A, de Leonibus C, Hanson D, et al. Pediatric perspective on pharmacogenomics. *Pharmacogenomics*. 2013;14(15):1889-1905. doi:10.2217/pgs.13.193
100. Hawcutt DB, Thompson B, Smyth RL, Pirmohamed M. Paediatric pharmacogenomics: an overview. *Arch Dis Child*. 2013;98(3):232-237. doi:10.1136/archdischild-2012-302852
101. Elzagallaai AA, Carleton BC, Rieder MJ. Pharmacogenomics in pediatric oncology: Mitigating adverse drug reactions while preserving efficacy. *Annu Rev Pharmacol Toxicol*. 2021;61:679-699. doi:10.1146/annurev-pharmtox-031320-104151
102. Maagdenberg H, Vijverberg SJH, Bierings MB, et al. Pharmacogenomics in pediatric patients: Towards personalized medicine. *Paediatr Drugs*. 2016;18(4):251-260. doi:10.1007/s40272-016-0176-2
103. Jacqz-Aigrain E, Rane A. Pharmacogenetics in pediatrics. In: Jacqz-Aigrain E, Choonara I, eds. *Pediatric Clinical Pharmacology*; 2006:161-176 Pharmacogenetics.
104. Krebs K, Milani L. Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. *Hum Genomics*. 2019;13(1):39. doi:10.1186/s40246-019-0229-z
105. Chenoweth MJ, Giacomini KM, Pirmohamed M, et al. Global pharmacogenomics within precision medicine: challenges and opportunities. *Clin Pharmacol Ther*. 2020;107(1):57-61. doi:10.1002/cpt.1664
106. Sing C-W, Cheung C-L, Wong ICK. Pharmacogenomics – how close/far are we to practising individualized medicine for children? *Br J Clin Pharmacol*. 2015;79(3):419-428. doi:10.1111/bcp.12338
107. Brown JT, Ramsey LB, van Driest SL, Aka I, Colace SI. Characterizing pharmacogenetic testing among children's hospitals. *Clin Transl Sci*. 2021;14(2):692-701. doi:10.1111/cts.12931
108. Aka I, Bernal CJ, Carroll R, Maxwell-Horn A, Oshikoya KA, van Driest SL. Clinical pharmacogenetics of cytochrome P450-associated drugs in children. *J Pers Med*. 2017;7(4):14. doi:10.3390/jpm7040014

109. Ramsey LB, Brown JT, Vear SI, Bishop JR, van Driest SL. Gene-based dose optimization in children. *Annu Rev Pharmacol Toxicol*. 2020; 60(1):311-331. doi:10.1146/annurev-pharmtox-010919-023459
110. Martin MA, Hoffman JM, Freimuth RR, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and Abacavir Dosing: 2014 Update. *Clin Pharmacol Ther*. 2014;95(5):499-500. doi:10.1038/clpt.2014.38
111. Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Human Leukocyte Antigen B (HLA-B) Genotype and Allopurinol Dosing: 2015 Update. *Clin Pharmacol Ther*. 2016;99(1):36-37. doi:10.1002/cpt.161
112. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. *Clin Pharmacol Ther*. 2017;102(1):37-44. doi:10.1002/cpt.597
113. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. *Clin Pharmacol Ther*. 2016;99(4):363-369. doi:10.1002/cpt.269
114. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update. *Clin Pharmacol Ther*. 2013;93(4):324-325. doi:10.1038/clpt.2013.4
115. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther*. 2018;103(2):210-216. doi:10.1002/cpt.911
116. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin Pharmacol Ther*. 2018;103(4):574-581. doi:10.1002/cpt.1004
117. Theken KN, Lee CR, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. *Clin Pharmacol Ther*. 2020; 108(2):191-200. doi:10.1002/cpt.1830
118. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clin Pharmacol Ther*. 2015;98(2):127-134. doi:10.1002/cpt.147
119. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. *Clin Pharmacol Ther*. 2013;94(3): 317-323. doi:10.1038/clpt.2013.105
120. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. *Clin Pharmacol Ther*. 2021;110(4):888-896. doi:10.1002/cpt.2149
121. Gonsalves SG, Dirksen RT, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes. *Clin Pharmacol Ther*. 2019;105(6):1338-1344. doi:10.1002/cpt.1319
122. Lima JJ, Thomas CD, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. *Clin Pharmacol Ther*. 2021;109(6): 1417-1423. doi:10.1002/cpt.2015
123. Desta Z, Gammal RS, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. *Clin Pharmacol Ther*. 2019;106(4): 726-733. doi:10.1002/cpt.1477
124. Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. *Clin Pharmacol Ther*. 2021;109(2):302-309. doi:10.1002/cpt.2008
125. Clancy JP, Johnson SG, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the Context of CFTR Genotype. *Clin Pharmacol Ther*. 2014;95(6): 592-597. doi:10.1038/clpt.2014.54
126. Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of Ondansetron and Tropisetron. *Clin Pharmacol Ther*. 2017;102(2):213-218. doi:10.1002/cpt.598
127. Muir AJ, Gong L, Johnson SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for IFNL3 (IL28B) Genotype and PEG Interferon-α-based Regimens. *Clin Pharmacol Ther*. 2014;95(2):141-146. doi:10.1038/clpt.2013.203
128. Relling MV, McDonagh EM, Chang T, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the Context of G6PD Deficiency Genotype. *Clin Pharmacol Ther*. 2014;96(2):169-174. doi:10.1038/clpt.2014.97
129. Ramsey LB, Johnson SG, Caudle KE, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1 and Simvastatin-induced Myopathy: 2014 Update. *Clin Pharmacol Ther*. 2014;96(4):423-428. doi:10.1038/clpt.2014.125
130. Goetz MP, Sangkuhl K, Guchelaar H-J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clin Pharmacol Ther*. 2018;103(5): 770-777. doi:10.1002/cpt.1007
131. Moriyama B, Obeng AO, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clin Pharmacol Ther*. 2017; 102(1):45-51. doi:10.1002/cpt.583
132. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther*. 2017; 102(3):397-404. doi:10.1002/cpt.668
133. Rahawi S, Naik H, Blake KV, et al. Knowledge and attitudes on pharmacogenetics among pediatricians. *J Hum Genet*. 2020;65(5): 437-444. doi:10.1038/s10038-020-0723-0
134. Roberts TA, Wagner JA, Sandritter T, Black BT, Gaedigk A, Stancil SL. Retrospective review of pharmacogenetic testing at an academic children's hospital. *Clin Transl Sci*. 2021;14(1):412-421. doi:10.1111/cts.12895
135. Reay WR, Cairns MJ. Advancing the use of genome-wide association studies for drug repurposing. *Nat Rev Genet*. 2021;22(10):658-671. doi:10.1038/s41576-021-00387-z
136. Adam de Beaumais T, Jacqz-Aigrain E. Chapter Eight – Pharmacogenetics: applications to pediatric patients. In: Brøsen K, Damkier P, eds. *Advances in Pharmacology: Pharmacogenetics*. Vol. 83. Academic Press; 2018:191-215.
137. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018;58(Suppl 10):S10-S25. doi:10.1002/jcph.1284
138. Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. *Br J Clin Pharmacol*. 2015;79(2):222-240. doi:10.1111/bcp.12441
139. Johnson D, Hughes D, Pirmohamed M, Jorgensen A. Evidence to support inclusion of pharmacogenetic biomarkers in randomised controlled trials. *J Pers Med*. 2019;9(3):42. doi:10.3390/jpm9030042
140. Nies AT, Niemi M, Burk O, et al. Genetics is a major determinant of expression of the human hepatic uptake transporter OATP1B1, but

not of OATP1B3 and OATP2B1. *Genome Med*. 2013;5(1):1. doi:10.1186/gm405

141. Emami Riedmaier A, Burk O, van Eijck BAC, et al. Variability in hepatic expression of organic anion transporter 7/SLC22A9, a novel pravastatin uptake transporter: Impact of genetic and regulatory factors. *Pharmacogenomics J*. 2016;16(4):341-351. doi:10.1038/tpj.2015.55
142. Klein K, Winter S, Turpeinen M, Schwab M, Zanger UM. Pathway-targeted pharmacogenomics of CYP1A2 in human liver. *Front Pharmacol*. 2010;1:129. doi:10.3389/fphar.2010.00129
143. Ortiz-Barahona V, Joshi RS, Esteller M. Use of DNA methylation profiling in translational oncology. *Semin Cancer Biol*. 2020; doi:10.1016/j.semcancer.2020.12.011
144. Liang Z, Kidwell RL, Deng H, Xie Q. Epigenetic N6-methyladenosine modification of RNA and DNA regulates cancer. *Cancer Biol Med*. 2020;17(1):9-19. doi:10.20892/j.issn.2095-3941.2019.0347
145. Zhao BS, Roundtree IA, He C. Post-transcriptional gene regulation by mRNA modifications. *Nat Rev Mol Cell Biol*. 2017;18(1):31-42. doi:10.1038/nrm.2016.132
146. Zhang J, Zhang Y-Z, Jiang J, Duan C-G. The crosstalk between epigenetic mechanisms and alternative RNA processing regulation. *Front Genet*. 2020;11:998. doi:10.3389/fgene.2020.00998
147. Wang ET, Sandberg R, Luo S, et al. Alternative isoform regulation in human tissue transcriptomes. *Nature*. 2008;456(7221):470-476. doi:10.1038/nature07509
148. Annalora AJ, Marcus CB, Iversen PL. Alternative splicing in the cytochrome P450 superfamily expands protein diversity to augment gene function and redirect human drug metabolism. *Drug Metab Dispos*. 2017;45(4):375-389. doi:10.1124/dmd.116.073254
149. Meyer UA, Zanger UM, Schwab M. Omics and drug response. *Annu Rev Pharmacol Toxicol*. 2013;53(1):475-502. doi:10.1146/annurev-pharmtox-010510-100502
150. Gliddon HD, Herberg JA, Levin M, Kaforou M. Genome-wide host RNA signatures of infectious diseases: discovery and clinical translation. *Immunology*. 2018;153(2):171-178. doi:10.1111/imm.12841
151. Aslam B, Basit M, Nisar MA, Khurshid M, Rasool MH. Proteomics: Technologies and their applications. *J Chromatogr Sci*. 2017;55(2):182-196. doi:10.1093/chromsci/bmw167
152. DrugBank. www.drugbank.ca. Accessed September 27, 2021.
153. Pang H, Jia W, Hu Z. Emerging applications of metabolomics in clinical pharmacology. *Clin Pharmacol Ther*. 2019;106(3):544-556. doi:10.1002/cpt.1538
154. Beger RD, Dunn W, Schmidt MA, et al. Metabolomics enables precision medicine: "A White Paper, Community Perspective". *Metabolomics*. 2016;12(10):149. doi:10.1007/s11306-016-1094-6
155. Hanna MH, Brophy PD. Metabolomics in pediatric nephrology: emerging concepts. *Pediatr Nephrol*. 2015;30(6):881-887. doi:10.1007/s00467-014-2880-x
156. Neavin D, Kaddurah-Daouk R, Weinshilboum R. Pharmacometabolomics informs pharmacogenomics. *Metabolomics*. 2016;12(7):17. doi:10.1007/s11306-016-1066-x
157. Baquero F, Nombela C. The microbiome as a human organ. *Clin Microbiol Infect*. 2012;18(Suppl 4):2-4. doi:10.1111/j.1469-0691.2012.03916.x
158. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res*. 2017;179:204-222. doi:10.1016/j.trsl.2016.08.002
159. Gromova M, Vaggelas A, Dallmann G, Seimetz D. Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape. *BiomarkInsights*. 2020;15:11772719209 7465. doi:10.1177/1177271920974652
160. 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. https://database.ich.org/sites/default/files/E16_Guideline.pdf. Accessed September 26, 2021.
161. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker qualification: Toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. *Clin Pharmacol Ther*. 2015;98(1):34-46. doi:10.1002/cpt.136
162. Forno E, Celedón JC. Epigenomics and transcriptomics in the prediction and diagnosis of childhood asthma: Are we there yet? *Front Pediatr*. 2019;7:115. doi:10.3389/fped.2019.00115
163. van Paemel R, Vlug R, de Preter K, et al. The pitfalls and promise of liquid biopsies for diagnosing and treating solid tumors in children: a review. *Eur J Pediatr*. 2020;179(2):191-202. doi:10.1007/s00431-019-03545-y
164. Allegaert K, Simons SHP, Tibboel D, Krekels EH, Knibbe CA, van den Anker J. Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: Filling the gaps beyond developmental pharmacology. *Eur J Pharm Sci*. 2017;109:27-31.
165. Kovar L, Schräpel C, Selzer D, et al. Physiologically-based pharmacokinetic (PBPK) modeling of buprenorphine in adults, Children and Preterm Neonates. *Pharmaceutics*. 2020;12(6):578. doi:10.3390/pharmaceutics12060578
166. Verscheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM. Physiologically-based pharmacokinetic models for children: Starting to reach maturation? *Pharmacol Ther*. 2020;211:107541. doi:10.1016/j.pharmthera.2020.107541
167. Wojtyniak J-G, Selzer D, Schwab M, Lehr T. Physiologically based precision dosing approach for drug-drug-gene interactions: A simvastatin network analysis. *Clin Pharmacol Ther*. 2021;109(1):201-211. doi:10.1002/cpt.2111
168. Wojtyniak J-G, Britz H, Selzer D, Schwab M, Lehr T. Data digitizing: Accurate and precise data extraction for quantitative systems pharmacology and physiologically-based pharmacokinetic modeling. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(6):322-331. doi:10.1002/psp4.12511
169. Fröhlich H, Balling R, Beerenwinkel N, et al. From hype to reality: data science enabling personalized medicine. *BMC Med*. 2018;16(1):150. doi:10.1186/s12916-018-1122-7
170. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010;9(3):203-214. doi:10.1038/nrd3078

How to cite this article: Neumann E, Schreeck F, Herberg J, et al. How paediatric drug development and use could benefit from OMICs: A c4c expert group white paper. *Br J Clin Pharmacol*. 2022;1-17. doi:10.1111/bcp.15216