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PEDIATRIC CLINICAL PHARMACOLOGY AND THE "THERAPEUTIC ORPHAN"

❖6696

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Despite present requirements for proof of safety and efficacy of new drugs, 78% of those marketed in the USA have not been so proved, and fully labeled for children (1). The principal reasons are the following.

1. The FDA's policy allows the marketing of drugs that have been approved in adults but not studied in children so long as labeling includes disclaimers and no instructions about pediatric use, thus creating the "therapeutic orphan" problem (2). The FDA has been urged recently to require premarketing pediatric studies of new drugs likely to be used in children (3), and guidelines have been developed for such studies (4). Also, proposed legislation would require preapproval studies in any special populations to which new drugs would have obvious application. In the meantime, the present situation forces physicians to prescribe agents that have not been proven to be safe or efficacious for children; this in itself is unreasonable, inequitable, and unethical.

2. Widespread misunderstanding of the ethical and legal implications hinders the only clinical experimental research from which reliable information can be obtained on the use of drugs in children—that which utilizes the child as the ultimate experimental subject. Enlightened investigators and institutional review boards can and have constructed pediatric clinical drug studies that can pass ethical and legal as well as scientific review. Important elements are prior informed consent from an individual qualified to act on behalf of the child, the assent of children capable of sufficient comprehension, and enrollment of a minor subject in risky or invasive studies only when the procedures or drug administration can be predicted to be for his/her own benefit (with rare exceptions).

[1]Dr. Judith Ganser assisted in the literature review.

3. Lack of broad categorical (as opposed to project-directed) support of pediatric clinical pharmacological research hinders the development of a core of qualified pediatric clinical pharmacology investigators and methodology for carrying out ethically acceptable pediatric drug studies. Because of the special ethical requirement that most drug studies in children be carried out in a therapeutic situation, it is crucial that there be special study procedures and units capable of focusing such techniques and appropriate pharmacologic expertise on clinical opportunities that present themselves. A number of investigators have utilized new approaches to the conduct of the type of clinical studies permissible in children, but more units with broad-based support are needed to capitalize upon the gains that have been made, and to accelerate progress toward the goal of ending the era of the therapeutic orphan.

This review examines the impact of recent pediatric clinical pharmacology studies upon the need for knowledge of pharmacokinetic parameters in pediatric patients to improve pediatric drug evaluations and usage. The aim is not only to define the current status of such clinical information, and the remaining gaps in our knowledge, but also to emphasize novel and ethically acceptable approaches that have been used. The pertinent data are scattered throughout the literature, and often indexed only according to the process or drug in question, discouraging attempts to provide comprehensive reviews. Our review is not exhaustive, but we hope adequate to serve the goals of providing a useful source of references and demonstrating the need for, and feasibility of, pediatric clinical pharmacology investigations.

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PHARMACOKINETICS DURING POSTNATAL HUMAN DEVELOPMENT

Recent data concerning certain pharmacokinetic parameters in infants, children, and adults are summarized in the three tables in this chapter. These particular parameters were selected because they (*a*) are most often selected by pediatric clinical pharmacology investigators, (*b*) have the most direct and practical usefulness in determining therapeutic regimens for pediatric use, and (*c*) are interdependent.

Developmental Overview

Our goal is not a comprehensive discussion of these pharmacokinetic parameters, but rather to evaluate them as markers of developmental pharmacokinetic changes and as promising tools for future studies.

Plasma Concentration Half-Life

Plasma half-life and the elimination constant (K_e) have the advantages of being easily measured and of describing the overall behavior of a circulating drug in a way that permits regulation of therapeutic regimens without the need to correct for body size.

The expected prolongation of half-life for most drugs during the period of early infancy was noted (Table 1), consistent with the clinically observed need for reduced

Table 1 Comparative apparent plasma drug half-life (hours) during postnatal human development[a]

Drug	Perinatal[b] Premature	Perinatal[b] Term	Newborn[c]	Infant[d]	Child[e]	Adult[f]	Reference(s)
Anti-Infectives							
Ampicillin	3.6–6.2	2.0–4.9	1.7–2.8			[1–1.8]	5, 6
Carbenicillin	6.6	2.9–4.7	1.5–2.2			[1]	5
Cephaloridin		3.7–5.4	2.1	1.1		[1–1.5]	6
Cephalothin	2.0	2.4		0.3	0.2–0.3	[0.5–0.9]	7, 8
Chloramphenicol	(15–22)	(8–15)			4	[2.3]	6
Clindamycin				—2.4–3.4—		4.5–4.8	9
					1.5–2.2	3.2–3.5	10
Colistimethate	2.6	2.6–9.0	2.3			[4.5]	6
Doxycycline	7.6	6.9		3.7	3.2–3.7	[12–22]	11
Gentamycin	5.1–5.9	3.8–5.5	2.3–3.9	2.3–2.9		(2–3) [2]	5, 12
Kanamycin	(8.4)–18	(5.7–7.5)	(3.8)–6			2 [2.2]	6, 13
Lymecycline		16.2		9.8	6.8	[(6–10)]	6
Methicillin	2.4–3.3	1.3–3.3	0.9–2.0	0.8–0.9		[0.4]	6
Neomycin	5.4		3.7				6
Oxacillin	1.6	1.5	1.2	1.1		0.7 [0.4–0.7]	6
Penicillin		3.2	1.7	1.4		[0.6–0.7]	5
Streptomycin	7.0					2.7 [1.9–2.7]	6
Sulfalene		135.6		53.9	51.0	63.3	6
Sulfisomidine			10.9	4.2			14
Sulfisoxazole		12.4	7.8	4.5		[6]	14
Tobramycin	8.1–8.7	4.6–6.1	3.9			2.2 [2]	15
Analgesics and/or Antipyretics							
Acetaminophen					(3.1, 3.4)	(2.0–2.6)	16
		3.5–4.9[g]			4.4–4.5[g]	3.6[g]	17
Antipyrine					6.6	13.6 [12–15]	18
Phenylbutazone[h]			27	17	20–40	76 [71–82]	18, 19
Propoxyphene					3.4	2.7 [3–7]	20
Salicylate[h]		(4.5–11.5)[g]			(2.0–3.1)	(2.0–3.5)	21
Cardiovascular drugs							
Diazoxide				(24)	(10–19)	(36, 24) [28]	22
Digoxin	90	(52, 26)	(35)–44	19–25	36–37	[31–40]	23
Sedatives/Anticonvulsants/Anesthetics							
Amobarbital		39				16 [21–25]	24
Carbamazepine		(8–28)			(14, 19)	[(18–55)]	25
Clonazepam					29	[(20–60)]	26
Diazepam	75	31			18	(20–42)	27
Dipropylacetate					9.4	(15.3)	28
Ethosuximide					30–36	[56]	29, 29a
Lidocaine[h]		3				[(1.2–2.2)]	30
Mepivacaine		9				[0.12]	31
Phenobarbital	(41)–380	102–259	(67–99)	44–86	53–64	[(53)–118]	32, 42
Phenytoin[h]		17–60			5	15 [21–29]	25, 33, 34
Miscellaneous							
Caffeine	(36–144)	80				3.5	35
Nortriptyline		(56)				(17) [27]	36
Theophylline	30				1.8–3.9	4.6–6.7	37–39
Tolbutamide		>30				7 [6–8]	40

[a] Means, or ranges of means, are given where possible; where individual values or ranges are used, they are in parentheses.

[b] First week of life, or first 2 weeks in prematures; *premature* includes up to 37 weeks' gestation and/or low birth weight (< 2.5 kg) infants regardless of gestational age.

[c] 1 week–1 month in term infants; 2 weeks–2 months prematures.

[d] Remainder of first year.

[e] 1–16 years.

[f] Adult values in brackets are from literature cited in above references or by Pagliaro & Bénet (41), and not from comparative studies in the same laboratories as the pediatric data.

[g] Determined from urinary excretion, rather than plasma levels.

[h] Dose-dependent kinetics. Values shown are for levels at or near the therapeutic, except for phenytoin, where the children had toxic levels and where different bases were used for infant $T_{1/2}$ in the studies shown.

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doses and extended interdose intervals in order to achieve blood levels comparable with those in adults. Elimination of drugs from the plasma is least likely to be delayed for those mainly excreted unchanged by filtration and most likely for those that are actively secreted. For drugs that undergo extensive metabolism, elimination of drugs from the plasma varies with the efficiency of the metabolic processes involved.

Prolongations were greatest in premature infants, and for the most part declined progressively with increasing maturation such that half-life is usually within 50% of that for the adult after 1–2 months of life. Unfortunately, data are lacking for half-lives beyond early infancy for drugs with the most extreme prolongations, for example, caffeine, chloramphenicol, and cephalothin.

Somewhat unexpected was the frequency with which the half-life was shorter in children than in adults. For some, the half-life was shorter than in adults even during infancy, in which case it was also shorter in childhood.

Apparent Distribution Volume

Few data are available concerning the early development of this parameter (Table 2).

Drugs such as digoxin, anticonvulsants, sedatives, and tranquilizers have distribution volumes considerably in excess of either total body water (TBW) or extracellular water (ECW) in pediatric subjects, as in adults. The majority of drugs have a larger distribution volume during infancy and early childhood than in the adult, but the reverse was true of some drugs. Age-dependent distribution volume differences usually disappear less rapidly than those of the half-life, but here there were no

Table 2 Apparent distribution volumes (liter/kg) of drugs during postnatal human development[a]

Drug	Perinatal		Newborn	Infant	Child	Adult	Study conditions[b]	References
	Premature	Term						
Clindamycin					12[c]	34[c]	Therapeutic	9
Diazepam		1.8			2.6	[0.7–2.6]	Study	27
Digoxin	7.7	(6.0, 8.4)		15.4	16.1	[5.8]	Therapeutic	23
Dipropylacetate					0.25	(0.15)	Therapeutic	28
Ethosuximide					0.69	[0.9]	Study	29
Gentamycin	—0.52–0.56—					[0.28]	Therapeutic	12
Kanamycin	0.59–0.78	0.49–0.81	0.51–0.63			[0.19]	Therapeutic	13
Lymecycline		(1.0, 1.1)	(1.0)	(1.4–1.8)	(1.8, 2.1)		? Study	6
Phenobarbital	(0.68)	0.94		0.81	0.61	[0.7]	Therapeutic	42
Phenylbutazone[d]			0.25	0.16	0.15–0.11	[0.02–0.15]	Study	19
Phenytoin					0.78	0.78	Poisoning	34
Sulfalene		0.47		0.36	0.20	0.22	? Study	6
Sulfisomidine			0.46	0.34	0.28		Study	14
Sulfisoxazole		0.45	0.34	0.35	0.29	[0.16]	Study	14
Theophylline	0.69				0.25–0.46	0.3–0.6	Therapeutic	37–39
Total body water	0.90–0.80	0.74–0.80	0.74	0.72–0.60	0.58–0.64	0.51–0.62		43
Extracellular water	0.60–0.42	0.44–0.42	0.40	0.32–0.27	0.19–0.27	0.16–0.19		

[a] See footnotes to Table 1.

[b] Refers to the means or purpose of drug administration: Therapeutic, study (nontherapeutic) purposes, or accidental poisoning.

[c] Expressed as liters per square meter body surface area.

[d] Dose-dependent kinetics. Values shown are for levels at or near the therapeutic.

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instances of reversal of the direction of age-related change from one stage of development to another.

The pattern for digoxin appears to be unique: its volume of distribution is only modestly expanded during early infancy, but is as much as threefold greater than in adults in the older infant and the child. The distribution volume for a number of drugs varies as development progresses in a manner that may be independent of the changes in body water compartments.

Additional simultaneous measurements of distribution volume and half-life would be particularly worthwhile for drugs having the most extreme or fluctuating age-related changes in either parameter and/or for which there are unusual dosage requirements for infants and children such as in the cases of dicloxacillin (44) and cloxacillin (L. Strebel, A. Dajani, A. Done, unpublished observations). Mathematical models for examining the interrelationships of changes in body water distribution, renal function, and protein binding are dealt with in detail elsewhere (43).

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Drug Metabolism Processes

Even the neonate has considerable ability to carry out a number of drug metabolism processes (Table 3). While some pathways appear to be active and even capable of compensating for other reduced processes, the rates of maturation appear to vary from one type of process to another. Oxidation and hydroxylation go on relatively early, but at a reduced rate during the newborn period. N-dealkylation may be less active early and perhaps takes somewhat longer to mature. Glucuronidation of hydroxylated derivatives is perhaps the most inefficient drug metabolic pathway during early development and may take longest to mature. Other conjugations occur early in development and assume greater importance as a result of the inefficiency of other processes.

Protein Binding

Most drugs thus far studied are bound less to infant or cord blood than to normal adult serum, including salicylate (50, 54), some penicillins (54, 56), phenobarbital (56), phenytoin (36, 56), cephazolin, cephadrin, clindamycin (57), theophylline (37), sulfonamides (58, 59), lidocaine, and bupivacaine (60). For several the binding is still less with fetal than with neonatal serum (56), and binding of most drugs by infant serum is reduced still further in the presence of hyperbilirubinemia (56, 58). In contrast, diazepam (54) and digoxin (23) bind similarly to infant and adult sera. At least salicylate may be less well bound to maternal than to infant serum (55).

CLINICAL STUDY APPROACHES IN CHILDREN

References in Tables 2 and 3 to the study conditions indicate that much or most of the pharmacokinetic information needed for adequate pediatric drug use and labeling can be obtained in the therapeutic situation in ways consistent with the aforementioned caveats concerning pediatric research. We have the impression that the present constraints not only have not impeded drug research in children, but also may have improved its quality by forcing improved planning, methods development, ingenuity, and attention to detail. The hallmark of the current approach is

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Table 3 Recent quantitative studies of drug metabolism during postnatal human development[a]

Drug (or substrate)	Metabolite (or process)	Units, time	Premature newborns	Term newborns	Older infants	Children	Adults	Study[b] conditions	Reference(s)
URINARY METABOLITES: as percentage of dose (*d*) or recovered metabolites (*m*)									
Acetaminophen	Unchanged	%*d*, 36 hr		3		4	2	Study	17
	Glucuronide			17		32-47	50		
	Sulfate			50		45-30	30		
				k=formation rate constant (hr^{-1}):					
	Unchanged	%*d*, 48 hr		2 *k*=0.005			[*k*=0.010]	Study	16
	Glucuronide			13 *k*=0.025			[*k*=0.171]		
	Sulfate			48 *k*=0.099			[*k*=0.076]		
	Conjugates	%*d*, 24 hr	14	39	52		[80]	Study	45
Salicylate	Unchanged	%*m*		2			[14]	Maternal	21
	Glycine conjugates	10-70 hr[c]		76			[50]		
	Glucuronide, Acyl			0			[<5-10]		
	Phenolic			13			[20][c]		
Salicylamide	Glucuronide	%*m*, 30 hr		19			[80]	Study	46
p-Aminobenzoate	Unchanged	%d, 24 hr	3	2	4	16		Study	45
	Acetate		27	22	36	16			
	Glucuronide		7	19	18	17			
	Glycine conjugates		13	27	28	47			
Benzoate Na	Glycine conjugates	%*d*, 6 hr	3	5	11	24		Study	45
Choramphenicol	Unchanged	%*d*, 24 hr		5-10			[5-15]	Therapeutic	47
	Glucuronide			ca 50			[85-95]		
Nortriptyline	Hydroxy	%*m*		(33-60)			(26-48)	Maternal	36
	Glucuronide	24-96 hr[c]		(40-67)			(52-74)		

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Table 3 *(Continued)*

Drug (or substrate)	Metabolite (or process)	Units, time	Premature newborns	Term newborns	Older infants	Children	Adults	Study[b] conditions	Reference(s)
Diazepam	Unchanged	%*d*, 24 hr	0.05	0.05		0.02		Study	27
	N-Demethyl		0.06	0.17		0.05[d]			
	Glucuronide		1.0	1.4		4.4			
	Hydroxy		0	0.3		1.5	(included in glucuronide fraction)		
Phenytoin	Hydroxy, then Glucuronide	%*m* 3-124 hr[c]		91-97			(99)	Maternal	25
		%*m*, 2-5d		88-99			[70]	Maternal	33
		%*m*, 6d		a b		> 99		Poison	34
Phenobarbital	Unchanged	%*m*		(70-42)			[10-25]	Therapeutic	48
	Hydroxy	a,72 hr b,72-192 hr		(19-26)			[Equal distribution]		
	Sulfate (of hydroxy)			(10-32)					
	Unchanged	%*m*, 24 hr		(62)				Maternal	49
	Hydroxy			(32)					
Caffeine	Unchanged	%*m*		(75,83)			(26)	Maternal	49
	Demethyl	24-48 hr[c]		(25,19)			(72)		
Lidocaine	Unchanged	%*m*		45			36	Maternal	30
	N-De-ethyl	0-24 hr[c]		30			10		
	De-amide, hydroxy			25			54		
Mepivacaine	Unchanged	%*m*		71			11	Maternal	31
	N-Demethyl	0-30 hr[c]		22			7		
	Hydroxy, then glucuronide			7			82		

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Table 3 (*Continued*)

Drug (or substrate)	Metabolite (or process)	Units, time	Premature newborns	Term newborns	Older infants	Children	Adults	Study[b] conditions	Reference(s)
Tolbutamide	Oxidized	%*d*, 36 hr		31			53	Study	38
Diazoxide	Unchanged	%*d*, 24 hr			(30)	(20)	(25-35)	Therapeutic	22
Digoxin	Unchanged	%*m*, 5 days	———	100	———		[74-90 +]	Therapeutic	23
BLOOD OR TISSUE ENZYME ASSAYS:[e] Amount metabolized per minute									
Aspirin	Esterase	nM/ml	8	11	13	14	13	Diagnostic samples	50
Acetylcholine	Esterase (RBC)	μM/ml	4.6-5.8	5.3	7-9	9-10	10	Samples of cord blood, from indwelling catheters, etc	51
Butyrylcholine	Esterase (plasma)	μM/ml	0.3-1.1	1.2	2.0-2.3	2.1-2.5	2.0		
Phenylacetate	Arylesterase (plasma)	μM/ml	6.5	8.4	19.5	24.2	27.8		
Paraoxon	Esterase (plasma)	nM/ml	3.6	3.4		6.1	7.3		
Procaine	Esterase (plasma)	nM/ml	1-7	7	8-9	10-11	10		
Cytochrome *c*	Reduction (liver)	nM/mg protein		(23)	(16-21)	(14,54)		Diagnostic biopsy	52

[a] See footnotes to Table 1.

[b] Refers to drug administration or means of procuring assay specimens: therapeutic, for study (nontherapeutic) purposes, maternal drug reaching fetus, accidental poisoning, diagnostic blood or biopsy specimens.

[c] Hours postpartum.

[d] Reflects greater excretion as glucuronide; formation of this and the hydroxylated metabolites was much reduced in infants compared with children.

[e] Enzyme activities demonstrated to be present in the fetus, and presumably postnatal enzyme activities as well, are not included, but have recently received thorough review (53).

maximization of the potential investigative benefits afforded by therapeutic or accidental exposures of infants and children to drugs deserving of pediatric study.

Valuable sources of pharmacokinetic data, in addition to direct treatment of sick children, include studies of drugs used in labor or delivery (30, 61, 62) and of drugs received by infants transplacentally as a result of treatment either of chronic maternal disease or symptoms (21, 25, 33) or pregnancy complications (24, 48). Instances of accidental overdosage of children (32, 61, 62) or pregnant women at term (36) offer unique opportunities to study drugs or doses that could not legitimately be given to infants or children.

Nontherapeutic administration of a drug specifically for study purposes in pediatric patients, though rarely needed, seems acceptable in certain instances when the drug is being employed as a substrate for studying drug metabolism processes or broad pharmacologic problems. It is probably possible to carry out such studies when the drug(s) and dose(s) are clearly safe and often used therapeutically in the same or similar subjects, and when the study techniques do not themselves introduce risk or pain to any major extent. Appropriate peer review and consents must always be obtained. Urinary excretion of metabolites after therapeutic doses has been used under such conditions to study the status in infants and children of the detoxification processes reflected by acetaminophen (16, 17) and salicylamide (46).

A variety of techniques have been employed to capture legitimate therapeutic opportunities for investigation. The authors rely upon ongoing collaborations and prior protocol development with the clinical subspecialists who have primary responsibility for most patient care. Others have done likewise and/or have taken advantage of requests for blood-level monitoring (63); have asked parturient women about the intake of drugs of interest prior to delivery (21), or have seized such other opportunities for exceptional studies as the use of otherwise sacrificed specimens of tissue obtained at surgery (64, 65), autopsy (23, 65), or therapeutic abortion (65, 66) or cerebropinal fluid obtained for diagnostic purposes (67, 68) for studies of drug distribution, and liver biopsy materials obtained for diagnostic purposes for sensitive assays of drug metabolism enzyme activities (52).

The most generally agreed upon needs are for improving the usefulness of noninvasive procedures. Micromethods are needed so that drug measurements can be made in blood sample sizes obtainable from capillary sources, and several have been devised that require only 10 to 100 μl of serum (7, 12, 22, 24, 25, 67), and sample size can be reduced further by use of whole-blood methods (37). The use of noninvasive sampling sources (that reflect blood concentrations) such as saliva for theophylline measurements (69) also deserves further pursuit. Invasiveness can be diminished by coordinating drug-study blood samples with those obtained for diagnostic purposes and by using samples obtainable from indwelling catheters when these are employed for clinical purposes. Umbilical cord blood can sometimes be used for neonatal studies.

Levy's (21) and Roberts' (17) groups have demonstrated the ability to use urine measurements to obtain much of the needed kinetic information for at least some drugs. Cumulative urinary excretion or areas under limited-sampling serum curves often suffice for bioavailability studies in children (23). The authors agree with

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Wilson (20) that where blood studies are essential, it is often satisfactory in the initial kinetic explorations to obtain limited sampling from each patient at different time intervals and to prepare scattergrams of random time intervals to approximate the profile of drug levels, in lieu of obtaining multiple samples. Pharmacokinetic predictions thus obtained can then be verified in larger therapeutic studies.

Some compromises are unavoidable, but the concern should not be with utilizing children for the initial and definitive establishment of a drug's disposition, but rather for determining whether infants or children differ significantly from adults. By the same token, efficacy should ordinarily be established in adults and pediatric studies used to verify applicability to children, a point that is often forgotten by investigators and regulatory agencies alike. The acceptability of invasive study procedures is also increased when the results can be used to regulate therapy for the individual; this necessitates a rapid turn-around time, which may be an acceptable price to pay for ability to perform the studies.

Therapeutic drug studies are undertaken usually only after adult studies have provided reasonable expectations of safety and benefit. One major safeguard stressed by a number of authors (12, 20, 67) is to leave the final decision regarding drug selection to the primary physician, when he is not the investigator, rather than with the investigator. As undesirable as concomitant medications may be, their avoidance is sometimes neither possible nor desirable in the sick patients used for pediatric studies, and it is essential that this be recognized by those who evaluate such studies particularly from a regulatory viewpoint. There is merit in obtaining kinetic studies early in the pediatric evaluation of a drug because this greatly assists further study design and provides best assurance of avoiding potentially dangerous underdosing or overdosing. It is sometimes possible in initial kinetic studies to substitute a single dose of the study drug for one of known safety and efficacy, so as not to subject the patient to undue jeopardy by prolonged exposure to an untested drug (70); the conventional "wash-out" usually sought in adult studies may not be possible.

Optimal studies in the therapeutic context require teamwork of pharmacologists, clinical specialists, and those with laboratory expertise, at least during the early stages of a drug's evaluation when it is essential to obtain sufficient kinetic data to assure the safest and most effective expansion of evaluations.

There is certainly merit in providing for more such units and in promoting individual projects. However, because of the magnitude and complexities of the pediatric drug therapy problems—involving old as well as new drugs—and the necessity for approaching most of them in the therapeutic situation, more categorical support of existing units that can provide the required types of comprehensive and sophisticated studies of large and diverse patient populations offers the greatest hope for rapid improvement in the therapeutic orphan problem.

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