·专题报道·

基于药物代谢酶和转运体基因组学的药物精准治疗

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摘要: 药物基因组学旨在研究药物效应 (药物体内过程、安全性和有效性) 的个体差异与基因变异 (药物代谢酶、转运体和药物靶点) 之间的关系。药物精准治疗是以药物基因组学为基础, 结合患者的其他个体情况实施量体裁衣式的药物治疗。本文总结了基于药物代谢酶和转运体基因组学的药物精准治疗的临床应用进展, 提出应重点关注的科学问题 (包括多基因和非遗传因素对药物效应的影响、治疗药物监测与药物基因组学检测的整合), 同时提出临床应用中面临的瓶颈问题及其相关对策。

关键词: 药物代谢酶; 转运体; 精准治疗; 药物基因组学; 组合药物基因组学; 表型转换

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Personalized dosing from perspective of pharmacogenomics of drug metabolizing enzymes and transporters

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Abstract: Pharmacogenomics is defined as research into the relationship between inherited genetic variations in drug metabolizing enzymes, transporters and targets and individual variations in person's response to drugs (fate of drug in human body, safety and efficacy). Personalized dosing is pharmacogenomics-based therapeutic regimen tailored to other individual characteristics. This article summarizes the progress in clinical application of personalized dosing from the perspective of pharmacogenomics of drug metabolizing enzymes and transporters, and proposes to draw attention to key scientific issues (e.g., the effect of multi-genes and non-genetic factors on drug effects, the integration of therapeutic drug monitoring and pharmacogenomics); meanwhile, bottle necks in the clinical application and corresponding strategies are proposed.

Key words: drug metabolism; transporter; personalized dosing; pharmacogenomics; combinatorial pharmacogenomics; phenoconversion

药物基因组学 (pharmacogenomics) 旨在研究药物效应 (药物体内过程、安全性和有效性) 的个体差异与药物代谢酶、转运体和药物靶点基因多态性之间的关系。药物精准治疗 (personalized dosing) 是以药物基因组学为基础, 根据患者的个体情况实施量体裁衣式的药物治疗 (即特定患者适合用什么药、精准预估药物效应和给药剂量、预测和预防药物毒性)。积极利用药物代谢与转运基因组学的知识, 可以增进疗效、减少药品不良反应以及降低药物治疗费用[1]。

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近五年来基于药物代谢酶和转运体基因组学的药物精准治疗成为精准医学的热点之一, 本文总结了该领域的临床应用进展。

1 具有临床指导意义的药物基因组学标志物

药物基因组学从基础到临床、从理论到实践、从群体到个体, 已经取得了可喜的成果。已有许多文献揭示药物代谢酶和转运体的基因多态性与药动学参数、疗效或药品不良反应发生率之间的关系。2016 年 3 月美国临床药物基因组学应用委员会 (Clinical Pharmacogenetics Implementation Consortium, CPIC) 更新了 33 个药物的药物基因组学应用指南, 其中涉及药物代谢转运的有 25 个 (表 1)[2]。

美国食品药物管理局 (Food and Drug Administration, FDA) 于 2013 年 1 月发布了《临床药物基因组学指导原则: 早期临床研究的上市前评价和对药品说明书的建议》[3], 对药品说明书中药物基因组学资料的描述有相关要求。“药物基因组学”会出现在“临床药理学”项下。当这种资料对安全有效用药有重要影响, 或遗传变异会导致限制药物使用、调整剂量、禁忌或警告时, 应该在药品说明书中加框警告, 适应证、用法用量、禁忌、警告、注意事项或药物相互作用中进行相关概述。例如, 在波立维®(硫酸氯吡格雷片) 药品说明书的加框警告部分可见描述“慢代谢者中的疗效降低。本品的疗效依赖于细胞色

Table 1 CPIC guideline for applications of pharmacogenomics associated with drug metabolism and drug transport. CPIC: Clinical Pharmacogenetics Implementation Consortium; UGT: Uridine diphosphate-glucuronosyl transferase; TPMT: Thiopurine *S*-methyltransferase; DYPD: Dihydropyrimidine dehydrogenase; CYP: Cytochrome P450; VKORC1: Vitamin K epoxide reductase complex subunit 1; SLCO1B1: Solute carrier organic anion transporter family member 1B1

Drug	Biomark	Clinical implications and guideline suggestion
Atazanavir	*UGT1A1*	Markedly decreased UGT1A1 activity would be observed in poor metabolizers of *UGT1A1**28/*28, *28/*37 or *37/*37, resulting in high likelihood of bilirubin-related discontinuation of atazanavir. Consider an alternative agent particularly where jaundice would be of concern to the patient.
Azathioprine, mercaptopurine, thioguanine	*TPMT*	Design the starting dose based on genotyping of *TPMT* in order to avoid severe myelosuppression. Consider alternative nonthiopurine immunosuppressant therapy for nonmalignant patients carrying *3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, or *3A/*4.
Capecitabine, fluorouracil, tegafur	*DPYD*	Design the starting dose based on genotyping of *DPYD* in order to avoid severe and possibly fatal toxicities. Consider alternatives for patients carrying *2A/*2A, *13/*13 or rs67376798A/ rs67376798A.
Citalopram, escitalopram, sertraline	*CYP2C19*	Genotyping of *CYP2C19* is recommended prior to prescribing. Consider an alternative drug not predominantly metabolized by CYP2C19 in order to avoid treatment failure in ultrarapid metabolizers carrying *17/*17 or *1/*17. Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 in poor metabolizers (*2/*2, *2/*3, *3/*3) in order to avoid the increased probability of side effects.
Desipramine, fluvoxamine, paroxetine, nortriptyline	*CYP2D6*	Genotyping of *CYP2D6* is recommended prior to prescribing. Consider an alternative drug not predominantly metabolized by CYP2D6 in order to avoid treatment failure in ultrarapid metabolizers carrying *CYP2D6**1/*1×N, *1/*2×N, or *2/*2×N. Consider a 25%−50% reduction of recommended starting dose or select alternative drug not predominantly metabolized by CYP2D6 in poor metabolizers (*3/*4,*4/*4, *5/*5, *5/*6) in order to avoid the increased probability of side effects.
Amitriptyline, imipramine, doxepin, clomipramine	*CYP2C19, CYP2D6*	Avoid the use of tricyclic antidepressants in ultrarapid, intermediate and poor metabolizers of *CYP2D6* and carriers of extensive metabolizers of *CYP2D6* also having ultrarapid metabolizers of *CYP2C19*. Consider 50% reduction of recommended starting dose in subjects with extensive metabolizers of *CYP2D6* also having poor metabolizers of *CYP2C19*. Utilize therapeutic drug monitoring to guide dose adjustments.
Clopidogrel	*CYP2C19*	Increased risk for adverse cardiovascular events would be observed in intermediate metabolizers (*CYP2C19**1/*2, *1/*3, *2/*17) and poor metabolizers (*CYP2C19**2/*2, *2/*3, *3/*3). Clinicians may consider alternative antiplatelet agents such as prasugrel and ticagrelor (if no contraindication).
Warfarin	*CYP2C9, VKORC1*	Genotyping of *VKORC1*-1639G>A, *CYP2C9**2 and *CYP2C9**3 could help to design the starting warfarin dose.
Codeine	*CYP2D6*	Genotyping of CYP2D6 is recommended prior to prescribing in order to avoid increased opioid toxicities in ultrarapid metabolizers (*CYP2D6**1/*1×N, *CYP2D6**1/*2×N), and insufficient pain relief in poor metabolizers (*CYP2D6**4/*4, *CYP2D6**4/*5, *CYP2D6**5/*5, *CYP2D6**4/*6). If necessary, consider alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics.
Phenytoin sodium	*CYP2C9*	Consider 50% reduction of recommended starting maintenance dose in order to avoid probability of toxicities due to reduced phenytoin metabolism and higher plasma concentrations.
Simvastatin	*SLCO1B1*	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin) for subjects with intermediate myopathy risk (*SLCO1B1**1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17), and subjects with high myopathy risk (*SLCO1B1**5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17). Routine creatine kinase surveillance should be considered.
Tacrolimus	*CYP3A5*	Initiate therapy with standard recommended dose for subjects with *CYP3A5**3/*3, *CYP3A5**6/*6, *CYP3A5**7/*7, *CYP3A5**3/*6, *CYP3A5**3/*7, or *CYP3A5**6/*7; however, a dose 1.5−2 times higher than standard dosing, but not to exceed 0.3 $mg \cdot kg^{-1} \cdot day^{-1}$, can be initiated among subjects with *CYP3A5**1/*3, *CYP3A5**1/*6, *CYP3A5**1/*7 or *CYP3A5**1/*1. Dosage should be adjusted according to therapeutic drug monitoring of tacrolimus plasma concentrations.

素 P450 (主要是 CYP2C19) 介导的药物代谢激活(见警告和注意事项)。采用氯吡格雷推荐剂量进行治疗的急性冠脉综合征或经皮冠脉介入的慢代谢者, 显示较 CYP2C19 功能正常患者的心血管事件发生率更高。目前已有确定 *CYP2C19* 基因型患者的检测方法, 这些方法可用于帮助确定治疗方案 (见临床药理学)。在确定为 *CYP2C19* 慢代谢的患者中, 应考虑替代的治疗或治疗方案 (见用法用量)”。2015 年 FDA 列出 140 种在药品说明书中提及药物基因组学生物标志物的药物, 其中涉及药物代谢酶的有 66 种药物, 但还没有收录转运体生物标志物[4]。有人评价了 FDA 药品说明书中药物基因组学检测的临床证据强度, 发现 15.1% 的说明书是有明确的临床实用性证据, 51.3% 的说明书相关描述仅仅是推荐用于临床决策参考[5]。

表 2 收录了近 5 年 PubMed 数据库荟萃分析证据支持或 FDA 药品说明书建议的药物代谢转运相关的药物基因组学标志物[3, 6−16]。

2　重点关注的科学问题

2.1　多基因因素　药物总的药理学作用并不是单基因性状, 而是由编码参与多种药物代谢途径、药物处置和药物效应的多种蛋白的若干基因决定的。单因素的考察可能不能很好地解释药动学的个体间差异。例如, 传统认为 *CYP2C9* 基因型是氟伐他汀血浆水平个体差异的主要决定因素, 作者发现 *CYP2C9**3 (1075A>C) 对氟伐他汀药时曲线下面积 (AUC) 的影响在统计学上具有极显著性 ($P<0.01$), CA 型携带者的 AUC 比 AA 型携带者平均高出 46.2%; 而且发现 *ABCB1* C3435T 显著影响了氟伐他汀的血浆峰浓度 (C_{max})。T 突变基因 (TT+CT) 携带者中的 C_{max} 比野生型纯合子 (CC) 平均高出 39.9% ($P<0.05$)[17]。也需要考虑多种转运体的共同影响, 例如研究发现 *ABCB1* 和 *ABCG2* 基因多态性对瑞舒伐他汀药动学有显著影响。*ABCB1* 1236TT 纯合子突变型个体中 C_{max} 和 AUC 显著高于 1236CT 杂合子突变型个体。*ABCG2* 421AA 纯合子突变体比野生型 421CC 个体有更高的

Table 2　Biomarks related with drug metabolism and transport based on meta-analysis evidence or FDA prescribing information. CYP: Cytochrome P450; VKORC1: Vitamin K epoxide reductase complex subunit 1; GSTP1: Glutathione *S*-transferase Pi 1; UGT: Uridine diphosphate-glucuronosyl transferase; TPMT: Thiopurine *S*-methyltransferase; MTHFR: Methylene tetrahydrofolate reductase; DYPD: Dihydropyrimidine dehydrogenase; NAT2: *N*-Acetyltransferase 2; SLCO1B1: Solute carrier organic anion transporter family member 1B1; ABCB1: ATP binding cassette subfamily B member 1; ABCG2: ATP binding cassette subfamily G member 2

Biomark	Clinical application	Genotype
CYP3A5	Predict the starting dose and chronic renal toxicity of tacrolimus, and dose of cyclosporin in renal transplant patients [6,7]	*CYP3A5**3
CYP2D6	Predict the efficacy of adjuvant tamoxifen for breast cancer [8], and safety of tramadol, amitriptyline, aripiprazole, perphenazine, tomoxetine, citalopram, clomipramine, doxepin, fluoxetine, vortioxetine, tomoxetine, venlafaxine, metoprolol, propafenone, quinidine or tolterodine in poor metabolizers and ultrarapid metabolizers receiving codeine [3]	Multi-allelic loci
CYP2C9	Predict the dose of celecoxib in poor metabolizers, warfarin in intermediate metabolizers and poor metabolizers[3]	*2/*2, *3/*3, *2/*3(celecoxib); *1/*3, *1/*2, *2/*2, *3/*3, *2/*3 (warfarin)
VKORC1	Predict the starting dose and drug toxicity of warfarin [3]	*VKORC1*-1639G>A
CYP2C19	Predict clopidogrel resistance, voriconazole dose and safety of citalopram and diazepam in poor metabolizers[3]	*CYP2C19**2, *CYP2C19**3
CYP1B1	Predict the anti breast cancer efficacy of paclitaxel [9]	*CYP1B1**3
GSTP1	Predict the efficacy of cisplatin and oxaliplatin [10]	*GSTP1* A313G
UGT1A1	Predict the toxicity of irinotecan (e.g., diarrhea and bone marrow suppression) [3], and nilotinib-induced hyperbilirubinemia [3]	*UGT1A1**28, *UGT1A1**6 (irinotecan); *UGT1A1**28 (nilotinib)
TPMT	Predict the efficacy and toxicity of mercaptopurine and azathioprine [3]	*TPMT**2 (G238C), *TPMT**3A (G460A/A719G), *TPMT**3B (G460A), *TPMT**3C (A719G)
MTHFR	Predict the relapse risk in acute lymphoblastic leukemiapatients receiving methotrexate [11]	*MTHFR* C677T
DPYD	Predict toxicity of 5-fluorouracil (gastrointestinal cancer) and capecitabine (recurrent breast cancer)[12]	*DPYD*c.1679T>G, c.1236G>A/HapB3, *DPYD**2A, c.2846A>T
NAT2	Predict hepatic toxicity of anti tuberculosis drugs [3]	*NAT2**4
SLCO1B1	Predict the probability of enalapril-induced cough [13], and down-regulation of simvastatin dose or therapeutic switch to other statins [14]	c.521T>C
ABCB1	Predict imatinib response in chronic myeloid leukemia patients [15] and drug response of platinum-based chemotherapy in non small cell lung cancer patients [10]	c.1236C>T, c.2677G>T/A, c.3435C>T
ABCG2	Predict the uric acid-lowering effect of allopurinol [16]	Q141K (rs2231142)

C_{max} 和 AUC[18]。

另外, 需要综合考虑药物代谢转运与药效学靶点多态性对药物效应的联合影响。例如, 美托洛尔主要经 CYP2D6 代谢, 美托洛尔在 *CYP2D6* 慢代谢者体内的血药浓度较高, 假如患者的 β1-受体敏感性强或受体数量较多, 则伴随高的疗效。假如受体敏感性差或受体数量少, 则疗效高但同时不良反应大。在应用同一个剂量后理论可产生 9 种不同的药物反应。代谢酶和受体均为野生型纯合子的个体将产生较高的疗效和最小的毒性; 相反, 两者均为纯合子突变基因型的个体则效应最低、毒性最大。组合药物基因组学 (combinatorial pharmacogenomics) 已开始用于指导药物精准治疗。例如, 与单基因测试相比, 集合 *CYP2D6*、*CYP2C19*、*CYP2C9*、*CYP1A2*、5-羟色胺转移蛋白基因 (*SLC6A4*) 和 5-羟色胺 2A 受体 (*HTR2A*) 的组合药物基因组学已被证实可以为抑郁症治疗提供更佳的临床有效性和成本效益[19]。周宏灏院士团队以高血压病的药物治疗为切入点, 创新性研发了国内第一张基因芯片。利用该基因芯片检测 6 个基因多态性 (*CYP2C9**3、*CYP2C19**2、*CYP2C19**3、*CYP2D6**10、β1-受体 Gly389Arg 和血管紧张素Ⅱ1 型受体 A1166C), 来进行高血压病的药物精准治疗。

2.2 非遗传因素 患者具有复杂性, 体现在生理、病理、医学因素 (多种疾病、疾病类型、多重用药、遗传因素、药品不良反应史、用药史) 、用药依从性、药品可及性、经济条件、健康素养和文化。一般认为, 遗传因素也只能解释 60%左右的个体间变异, 因此, 广义的药物精准治疗必须考虑到非遗传因素的影响, 不能只局限于药物基因组学检测, 而是应该以患者为中心、团队协作的综合干预, 才能制定出适合于个体的精准方案。

Kim 等[20]评价了 2 188 名经皮冠状动脉介入治疗 (PCI) 术后接受氯吡格雷治疗患者的 *CYP2C19* 基因型对临床结果的影响, 结果发现 *CYP2C19* 慢代谢基因型与急性心肌梗死患者亚组中的心脑血管不良事件密切相关 (风险比为 2.88, P = 0.011), 但在稳定型心绞痛患者亚组中却没有观察到这种相关性。作者研究了匹伐他汀酸和酯的药动学个体间差异的分子机制, 发现除 *CYP2C9**3, *ABCB1* G2677T/A, *SLCO1B1* c.521T>C, *SLCO1B1* g.11187G>A 和 *SLCO1B1**17 外, 性别对个体间差异也有重要贡献。与 521TT 男性受试者相比, *SLCO1B1* 521TT 女性受试者中匹伐他汀酯的 C_{max} 和 $AUC_{(0-\infty)}$更高[21]。

以药物基因组学为基础, 开展群体药动学 (population pharmacokinetics) 研究和模型构建, 可能是解决复杂患者药物精准治疗的重要方向。例如, van Schie 等[22]给出了相应的公式, 揭示了苯香豆素的平均维持剂量的平方根与患者的基因型 (*CYP2C9* 和 *VKORC1*)、年龄、身高、体重、是否女性、是否合并使用胺碘酮之间的定量关系。Tan 等[23]建立了中国心脏瓣膜置换患者中华法林的剂量估算方法, 华法林维持剂量与 *VKORC1*-1639G>A、*CYP2C9**3、体表面积、年龄、能引起 INR 增高的合并用药个数、吸烟习惯、术前中风史和高血压密切相关。应用该模型可预测华法林维持剂量个体间差异的 56.4%。

在临床实践中发现表型转换 (phenoconversion) 现象, 多发生于治疗药物对代谢酶或转运体有明显抑制作用的情况。因此, 单一依赖基因型检测, 有时会误导临床决策[24, 25]。研究显示, 在接受文拉法辛缓释制剂治疗长达 8 周的 900 名抑郁症患者中, 在不是 *CYP2D6* 慢代谢基因型的 865 名患者中有 24%的患者变成了慢代谢表型。CYP2D6 慢代谢表型的发生率是慢代谢基因型发生率的 7 倍, 机制是文拉法辛是 CYP2D6 强抑制剂[26]。CYP2C19 也存在表型转换, 连续服用奥美拉唑或埃索美拉唑 4 周的受试者中 CYP2C19 慢代谢表型的发生率是慢代谢基因型发生率的 10 倍[27]。也就是说, 药物代谢酶和转运体介导的药物相互作用对药物精准治疗的实施有重要影响。恰当的合并用药可以为药物精准治疗所用。例如, 奥美拉唑竞争性抑制肝移植患者中他克莫司经 CYP3A4 的代谢, 在 CYP2C19 慢代谢者中这种影响尤为突出。因此, 合用奥美拉唑时他克莫司的药物精准治疗有必要同时检测 *CYP2C19**2、*CYP2C19**3 和 *CYP3A5**3。然而, 选择雷贝拉唑、泮托拉唑就可以降低与他克莫司相互作用的风险, 而且不受 *CYP2C19* 基因型影响[28]。

2.3 药物基因组学与治疗药物监测的整合 治疗药物监测 (therapeutic drug monitoring, TDM) 是指在临床药物治疗过程中, 观察药物疗效的同时, 定时采集患者的血液 (有时采集尿液、唾液等样本), 测定其中的药物浓度, 以药动学和药效学基础理论为指导, 根据患者的具体情况, 拟定给药方案。根据药物基因组学标志物测试结果, 设定一个初始治疗剂量, 然后通过 TDM, 进一步优化个体化用药方案, 使疗效最大化和不良反应最小化。欲使临床效益最大化, 药物基因组学的检测宜在治疗前或疗程的早期阶段进行。

这种药物基因组学与 TDM 的整合已经在伏立康唑、硫嘌呤类药物、镇痛药物和肾移植抗排异药物的精准治疗中发挥重要作用[29−32]。例如, *CYP2C19* 基因

型与伏立康唑血药浓度密切相关, 而后者又与伏立康唑的抗真菌临床疗效和不良反应显著相关。伏立康唑的目标治疗谷浓度为 2～6 $mg·L^{-1}$, 在携带超快代谢者基因 *CYP2C19**17 的个体中通常达不到治疗谷浓度。TDM 结果显示, 治疗谷浓度低于 0.2 $mg·L^{-1}$ 的个体中超快代谢者基因发生频率显著高于对照组。一名 62 岁的急性髓性白血病患者因疑似播散性真菌感染而接受伏立康唑治疗。首日剂量为一天两次, 每次 400 mg。次日起一天两次, 每次 200 mg。5 天后 TDM 显示谷浓度低于 0.3 $mg·L^{-1}$; 改用静脉给予伏立康唑(首次负荷剂量为 6 $mg·kg^{-1}$, 然后一天两次, 每次 5 $mg·kg^{-1}$), 4 天后谷浓度为 0.5 $mg·L^{-1}$。药物基因组学检测显示患者属于超快代谢者基因纯合子 *CYP2C19**17/*17 携带者, 这是导致应用高剂量伏立康唑后谷浓度仍低的主要原因。治疗方案改为静脉用卡泊芬净, 病情逐渐改善, 出院后以口服泊沙康唑序贯治疗。这个案例提示, 单纯实施 TDM, 可能不能及时达到伏立康唑的目标治疗浓度, 存在延误病情的风险; 而用药前进行药物基因组学测试, 一旦显示超快代谢者基因, 医生可第一时间改用替代药物[29]。对于硫嘌呤类药物而言, 药物基因组学检测与 TDM 的整合有三方面益处, 即检出巯基嘌呤甲基转移酶(TPMT) 极低活性或酶缺失的个体并启用替代药物治疗方案、根据硫唑嘌呤代谢物浓度来监测患者的用药依从性、以及识别具有耐药性高风险的患者 (人红细胞内硫嘌呤药物活性毒性代谢物 6-甲巯基嘌呤核苷酸与 6-硫鸟嘌呤核苷酸浓度比值≥20)[30]。Manvizhi 等[32]报道的一个案例强调了用药前药物基因组学检测结合疗程中持续进行 TDM 的重要性。肾移植后患者接受他克莫司、霉酚酸钠、激素三联的标准免疫抑制抗排异治疗。他克莫司初始剂量为 5.5 $mg·d^{-1}$, TDM 显示谷浓度 30 $ng·mL^{-1}$, 经过连续 4 次剂量下调, 谷浓度仍持续高于推荐治疗浓度范围。在移植后一年, 剂量已下调到 2 $mg·d^{-1}$, 采用有限采样法估算 AUC 为 140.9～165.6 $\mu g·h·L^{-1}$。2 年后由于同时接受了环丙沙星治疗, AUC 增加到 281.7 $\mu g·h·L^{-1}$; 停用环丙沙星一周后 AUC 降至 217.3 $\mu g·h·L^{-1}$。4 年后经患者知情同意后进行药物基因组学检测, 发现患者携带 *CYP3A5**3 (GG) 和 ABCB1-2677 (TT) 纯合子突变基因, 这是移植后一年内他克莫司谷浓度持续高于治疗浓度范围的主要原因。

3　生物标志物临床应用中面临的瓶颈问题和对策

在个体化用药的大背景下, 随着高特异性、高通量及高灵敏度的基因检测新技术的快速发展, 具体的分析技术问题已经不再是难题。然而, 证据级别高的或公认的药物基因组学检测项目在临床应用还很少, 其瓶颈在于检测项目尚未纳入医保范围, 使得患者不愿意支付额外的医疗费用而接受测试。其次, 药物基因检测的一些试剂还没有获得国家食品药品监督管理局注册证, 这两大原因导致不少医院的药物精准治疗仅仅停留在科研水平, 没有真正投入临床应用。建议有关部门出台相应的法规, 制定标准的实验室检测体系, 规范个体化治疗检测市场, 理顺价格支付机制, 切实为药物精准治疗的推广而保驾护航。

相对来说, 为避免严重不良反应的药物基因组学测试项目更受临床医生欢迎, 从表 1 和表 2 也可见, 基于安全性的药物基因组学检测项目比基于疗效预测的项目要多, 因此, 围绕治疗安全性的生物标志物挖掘与应用, 是药物精准治疗在临床推广的突破口。

合理用药强调安全、有效、经济、适当。因此, 药物经济学也是开展药物精准治疗所必须考虑的实际因素。系统评价显示, 氯吡格雷用药前的 *CYP2C19* 基因检测、阿巴卡韦用药前的人类白细胞抗原 *HLA-B**5701 检测、卡马西平用药前的 *HLA-B**1502 和 *HLA-A**3101 检测、以及别嘌醇用药前 *HLA-B**5801 检测被证实具有成本效益, 而对于硫嘌呤药物用药前 *TPMT* 检测、香豆素类药物用药前 *CYP2C9* 和 *VKORC1* 检测、甲氨蝶呤用药前 *MTHFR* 检测是否具有经济学意义, 结论尚未统一[33]。Donnan 等[34]也证实, 与基于体重的给药方案相比, 急性淋巴细胞性白血病儿童患者中基于 *TPMT* 基因型检测或基于 TPMT 酶活性检测的给药方案并不具有成本效益。更有研究表明, 香豆素类药物用药前药物基因组学检测的临床执行率依赖于检测的成本以及新型口服抗凝药的可及性。与华法林相比, 一些新颖的口服抗凝药无需在用药前进行药物基因组学检测[35]。也有人提出对需要使用口服抗凝药的房颤患者进行用药前药物基因组学检测, 根据基因检测结果对患者进行分诊。假如患者具有对华法林敏感性正常的基因型 (*CYP2C9**1/*1 和 *VKORC1* G/A), 则选择使用华法林; 假如患者具有对华法林敏感性高 (*CYP2C9**2、*CYP2C9**3 或 *VKORC1* A/A) 或敏感性低 (*VKORC1* G/G 且 *CYP2C9**1/*1) 的基因型, 则选择新颖口服抗凝药(如达比加群、利伐沙班、阿哌沙班)。与常规接受华法林抗凝的治疗模式相比, 基于药物基因组学的分诊模式具有更好的成本–效果比[36]。随着药物精准治疗理念的推行, 未来将会有更多药物经济学研究来为政府和临床决策提供证据。目前而言, 担心成本效

益问题仍是影响开展基于药物代谢酶和转运体基因组学的药物精准治疗的一个制约因素。美国一家基因检测技术公司评价了药物基因组学检测用于接受 5 种或 5 种以上药物的长期照护患者精准治疗的经济获益, 发现平均每个患者每年节约成本 621 美元[37]。该研究提供了一个重要启示, 即基于药物基因组学的精准治疗可在特殊群体中优先应用。

另外, 一些生物标志物在临床证据总体级别不高, 还需要通过开展进一步的基础研究和大样本量的数据分析来论证。荟萃分析通过合并资料而增大样本量, 可增加结论的可信度, 解决研究结果的不一致性。因此, 可尝试开展药物基因组学检测临床价值的荟萃分析研究。

4 结语

精准医学开启了个体化治疗新时代。基于药物代谢酶和转运体的药物精准治疗, 具有重要的临床意义和应用前景[38]。应重点关注多基因和非遗传因素对药物效应的影响, 重视 TDM 与药物基因组学检测的整合, 同时需解决临床应用中面临的瓶颈问题。临床上的药物精准治疗涉及药物表观基因组学、药物基因组学、药物代谢学、生物统计学、临床药理学、药物治疗学和药物经济学等, 因此, 需要多学科交叉, 基础与临床协同研究, 加强研发和挖掘证据级别高的新的生物标志物, 积极推动临床转化应用, 为临床药物精准治疗提供依据。

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