

**STUDI PUSTAKA****PENDEKATAN FARMAKOLOGI KLINIS MELALUI  
FARMAKOGENOMIK PADA ERA PENGobatan  
PRESISI**

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**Abstrak**

Efek farmakologi suatu obat dapat bervariasi pada tiap individu, yang pada kondisi merugikan dapat menyebabkan morbiditas bahkan mortalitas. Kondisi yang merugikan tersebut dikenal sebagai *adverse drug reaction* (ADR). Salah satu kondisi yang dapat berkontribusi terhadap kejadian ADR adalah variabilitas genetik. Adanya variabilitas genetik, menjadi salah satu perhatian perkembangan ilmu farmakologi melalui farmakogenomik. Ilmu ini mempelajari pengaruh gen terhadap respon obat pada individu. Adanya farmakogenomik diharapkan dapat menghasilkan pengobatan yang presisi sehingga meningkatkan efektivitas dan keamanan penggunaan obat. Beberapa gen telah diidentifikasi berperan terhadap perubahan kadar obat di dalam darah melalui aspek farmakokinetik serta efek obat terhadap tubuh (farmakodinamik). Adanya perubahan farmakokinetik dan farmakodinamik berpotensi menyebabkan keadaan subterapeutik maupun menghasilkan efek toksik. Tujuan studi pustaka ini untuk memberikan ketersediaan informasi variasi genetik yang berpotensi mempengaruhi respon pengobatan, sehingga diharapkan dapat menunjang penerapan pengobatan yang lebih presisi.

**Kata kunci:** CYP, farmakogenomik, obat, pengobatan presisi

**Abstract**

*One of the factors contributing to patient morbidity and death is the variable variability in treatment response. Adverse drug responses (ADRs) or subtherapeutic effects are possible in certain patients during medication administration. Genetic variation is among the numerous variables that contribute to this condition. Pharmacogenomics is the study of how genes influence an individual's response to drugs. The goal of pharmacogenomics is to optimize*



*treatment for the patient. It has been established that a number of genes are associated with drug response, affecting both the direct effects of drugs (pharmacodynamics) and their blood levels (pharmacokinetics). Modifications to a medication's pharmacokinetics and pharmacodynamics may result in toxicity or reduce its efficacy. In order to enhance the precision of pharmacotherapy techniques, this study aims to elucidate the availability of data on genetic variants known to influence medication response.*

**Keywords:** CYP, drug, pharmacogenomics, precise medicine

## PENDAHULUAN

Adverse drug reaction (ADR) merupakan salah satu penyebab morbiditas bahkan mortalitas yang dapat menjadi beban tambahan pelayanan sistem kesehatan (Akhideno et al., 2018). Berdasarkan laporan ADR global, terdapat sekitar 15 juta kasus yang dilaporkan sejak tahun 1957 hingga 2018. Namun, tidak semua negara berkontribusi dalam laporan ini, sehingga diyakini bahwa kejadian ADR jauh lebih besar daripada yang dilaporkan (T P, 2009). Studi yang dilakukan oleh Chan, dkk (2018) memperkirakan bahwa biaya perawatan rumah sakit akibat ADR mencapai US\$570,400 per 1000 pasien. Biaya akibat ADR menghabiskan sekitar 5% dari total dana kesehatan di Singapura (Chan et al., 2019). Diperkirakan lebih dari 50% total kasus ADR merupakan kasus yang dapat dicegah (Kalyani and Srihitha, 2017). Variabilitas respon obat interindividu merupakan salah satu faktor yang dapat berkontribusi terhadap kejadian ADR. Variabilitas respon ini dapat didasari oleh perbedaan genetik setiap individu (Cacabelos et al., 2019). Di

sisi lain, variabilitas genetik juga dapat menyebabkan perubahan kadar obat di bawah kadar terapeutik (Westervelt et al., 2014). Hal ini dapat menghasilkan pengobatan yang tidak optimal (Epstein et al., 2010; Lloberas et al., 2017).

Dalam beberapa tahun terakhir, farmakogenomik menjadi salah satu fokus pengembangan farmakologi (T P, 2009), yaitu cabang ilmu farmakologi yang mempelajari kontribusi faktor genetik terhadap variasi respon obat (Katzung, 2018). Farmakogenomik berkembang menjadi modalitas sebagai pertimbangan untuk mencegah ADR. Selain itu, pencegahan ADR juga berdampak positif pada efisiensi biaya (Akhideno et al., 2018; Weinshilboum and Wang, 2017).

Saat ini, telah banyak studi yang mendukung pemilihan regimen obat berdasarkan status genetik pasien (Cacabelos et al., 2019; Di Sanzo et al., 2017; Kim et al., 2017; T P, 2009). Pemilihan regimen didasarkan pada profil genetik individu terhadap profil farmakokinetik maupun farmakodinamik obat. Dengan



pendekatan ini, pengobatan menjadi spesifik terhadap tiap individu untuk mencapai efikasi dan keamanan yang lebih presisi atau dikenal juga sebagai *personalized medicine* (Weinshilboum and Wang, 2017). Melalui tulisan ini, penulisan bermaksud memaparkan ketersediaan informasi mengenai hubungan variasi genetik individu terhadap respon obat tertentu selanjutnya dapat digunakan untuk meningkatkan ketepatan strategi pengobatan.

## PEMBAHASAN

### Variabilitas Interindividu

Variabilitas individu merupakan salah satu faktor yang berkontribusi terhadap tercapainya efek terapeutik maupun munculnya efek samping suatu agen farmakologi. Hal ini disebabkan karena variabilitas genetik dapat terjadi pada level farmakokinetik maupun level farmakodinamik, bahkan fungsi sistem imun, seperti *human leukocyte antigen* (HLA) (Katzung, 2018). Pada level farmakokinetik, variabilitas dapat terjadi pada enzim pemetabolisme obat dan transporter protein. Sedangkan, pada level farmakodinamik, variabilitas terjadi pada protein target obat seperti reseptor, enzim, dan protein intraseluler (Lam, 2019). Variabilitas individu yang terjadi pada  $\geq 1\%$  populasi disebut sebagai polimorfisme (Brunton et al., 2017; Katzung, 2018).

Polimorfisme enzim pemetabolisme obat secara garis

besar dibedakan atas dua, yaitu polimorfisme sitokrom (CYP) dan non-CYP. Status metabolisme individu bergantung terhadap alel enzim tersebut. Sehingga, sangat banyak varian genotip yang dapat menentukan status metabolisme individu (Manikandan and Nagini, 2017). Polimorfisme pada CYP melibatkan beberapa CYP seperti 2D6, 2C19, 2C9, 2C8, 3A4, 3A5, 3A7, 4F2, 2B6, 2A6, dan 1A2 (Lam, 2019). Status metabolisme dikelompokkan menjadi empat kelompok, yaitu *poor metabolizer*, *intermediate metabolizer*, *extensive metabolizer*, dan *ultra-rapid metabolizer*. *Extensive metabolizer* dianggap sebagai fenotip normal (Brunton et al., 2017; Katzung, 2018). Polimorfisme pada enzim pemetabolisme obat non-CYP, juga memiliki peran dalam metabolisme dan proses eliminasi obat. Diantaranya *UDP-glucuronosyl transferase* (UGT), *thiopurine-S-methyltransferase* (TPMT), *dihydropyrimidine dehydrogenase* (DPD), *N-acetyltransferase* (NAT), dan *glutathione-s-transferase* (GST) (Lam, 2019).

Polimorfisme pada level transporter protein dapat terjadi pada kelompok transporter efluks maupun influks. Kelompok transporter efluks meliputi *adenosine triphosphate-binding cassette* (ABC) dan kelompok transporter influks meliputi *uptake solute carrier* (SLC) (Lam, 2019). Namun, polimorfisme yang



dianggap bermakna secara klinis oleh *International Transporter Consortium* (ITC) adalah ABCBG2 (BCRP) dan SLCO1B1 (OATP1B1) (Yee et al., 2018).

Fenotip dari variasi genetik terhadap protein target obat juga dapat mempengaruhi efek suatu obat (Goldstein et al., 2003). Sebagian besar obat memberikan efek terapeutik ketika berinteraksi dengan reseptornya, namun adanya variasi genetik pada reseptor obat akan menyebabkan perubahan efek yang dihasilkan. Beberapa reseptor target obat memiliki variabilitas individu, seperti *epidermal growth factor receptor type 2* (HER2), *adrenoceptor  $\beta$ -1* (ADRB1), *adrenergic  $\alpha$ 2C-receptor* (ADRA2C), reseptor *5-hydroxytryptamine* (5-HT), reseptor dopamin D3 (DRD3), dan  *$\mu$ -opioid receptor* (MOR) (Lam, 2019). Selain itu, adanya variabilitas gen pengkode enzim lain yang terlibat dalam mekanisme kerja obat juga mempengaruhi efek suatu obat. Seperti VKORC1 dan *catecho-O-methyltransferase* (COMT).

### Aplikasi Klinis Farmakogenomik

Beberapa area keilmuan dalam dunia kedokteran menjadi pusat pengembangan dan penerapan farmakogenomik. Onkologi, kardiologi, psikiatri, dan manajemen nyeri merupakan area pengembangan farmakogenomik yang telah eksis saat ini (Di Sanzo et al., 2017; Kim et al.,

2017; Lam, 2019). Selain itu, *Food and Drug Administration* (FDA) telah mengeluarkan rekomendasi terapi berdasarkan dengan pendekatan farmakogenomik yang dapat diakses melalui tautan (<https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>) (Food and Drug Administration, 2020). Berdasarkan daftar obat yang beredar di Indonesia, pendekatan farmakogenomik dapat dilakukan pada beberapa obat (Tabel 1 dan 2).

Obat-obat ini dihubungkan dengan peningkatan kadar obat di dalam darah yang meningkatkan risiko terjadinya efek yang tidak diinginkan berdasarkan karakteristik obat tersebut (Food and Drug Administration, 2020). Adapun obat-obat lainnya yang telah didukung oleh studi terkait efek sampingnya pada manusia (Tabel 2).

Terdapat beberapa rekomendasi pemeriksaan genetik dalam penerapan pendekatan farmakogenomik di pelayanan kesehatan. Seperti pemeriksaan gen CYP2C9 dan VKORC1 pada pemberian warfarin untuk menentukan dosis presisi dan mencegah efek samping, seperti perdarahan (Katzung, 2018; Kim et al., 2017). Pemeriksaan genotip CYP2C19 pada pasien yang direncanakan menggunakan clopidogrel untuk mencegah trombosis (Kim et al., 2017). Pemeriksaan NAT2 pada pasien yang



akan mendapatkan isoniazid guna optimalisasi dosis dan pencegahan toksisitas (Chan et al., 2017). Lebih lanjut, termasuk pemeriksaan HER2

pada pasien kanker payudara untuk penentuan pilihan terapi dengan atau tanpa trastuzumab (Carlson et al., 2006).

**Tabel 1.** Obat-Obat dengan Potensi Efek yang Tidak Diinginkan dan Rekomendasi Penggunaan Obat Sesuai Pendekatan Farmakogenomik

| Obat          | Sitokrom | Fenotip   | Rekomendasi  |
|---------------|----------|---|--|
| Amfetamin     | CYP2D6   | <i>poor metabolizer</i><br>(de la Torre et al., 2012) | -  |
| Aripiprazole  | CYP2D6   | <i>poor metabolizer</i>                               | Diberikan separuh dosis normal (Dean and Kane, 2021)   |
| Atomoxetine   | CYP2D6   | <i>poor metabolizer</i>                               | Dimulai dengan dosis rendah 0,5 mg/kgBB, kemudian lanjutkan dengan target kadar obat mendekati 400 ng/ml (Dean, 2020)  |
| Brexpiprazole | CYP2D6   | <i>poor metabolizer</i>                               | Diberikan separuh dosis normal (PharmKGB, 2023)  |
| Carvedilol    | CYP2D6   | <i>poor metabolizer</i>                               | Titration naik dosis perlahan sampai target terapi tercapai (Dean, 2018)   |
| Clobazam      | CYP2C19  | <i>intermediate</i> atau <i>poor metabolizer</i>      | Dosis awal 5 mg/hari kemudian titrasi sesuai respon klinis hingga maksimal 20 mg/hari untuk pasien dengan berat badan $\leq 30$ kg; 40 mg/hari untuk pasien dengan berat badan $>30$ kg (Dean, 2019) |
| Piroxicam     | CYP2C9   | <i>intermediate</i> atau <i>poor metabolizer</i>      | Ganti obat alternatif lainnya (PharmKGB, 2023)   |
| Vortioxetine  | CYP2D6   | <i>poor metabolizer</i>                               | Inisiasi dengan 50% dosis normal, kemudian titrasi sampai maksimal 10 mg (PharmKGB, 2023)  |

**Tabel 2.** Obat-Obat dengan Potensi Efek yang Tidak Diinginkan



| Obat                 | Gen                  | Alel/Fenotip   | Jenis Efek   |
|----------------------|----------------------|--|--|
| <b>Allopurinol</b>   | HLA-B                | *58:01 allele positive                                       | Sindrom Steven Johnson/ <i>toxic necrotizing epidermolysis</i> (Fan et al., 2017)  |
| <b>Azathioprine</b>  | TPMT dan/atau NUDT15 | <i>intermediate</i> atau <i>poor metabolizer</i>             | Toksisitas sumsum tulang, intoleransi saluran cerna (Liu et al., 2015)   |
| <b>Capecitabine</b>  | DPYD                 | <i>intermediate</i> atau <i>poor metabolizer</i>             | Toksisitas gastrointestinal dan hematologi (Si et al., 2014)   |
| <b>Carbamazepine</b> | HLA-A;<br><br>HLA-B  | HLA-A: *31:01 alel positif<br><br>HLA-B: *15:02 alel positif | <i>mild rash maculopapular exanthema</i> (MPE), <i>hypersensitivity syndrome</i> (HSS), Sindrom Steven Johnson (SSJ)/ <i>toxic necrotizing epidermolysis</i> (NET); SSJ/NET (Fan et al., 2017; Genin et al., 2014)   |
| <b>Celecoxib</b>     | CYP2C9               | <i>poor metabolizer</i>                                      | Perdarahan gastroduodenal (Pilotto et al., 2007)   |
| <b>Citalopram</b>    | CYP2C19              | <i>poor metabolizer</i>                                      | Mual, muntah, <i>drowsiness</i> (Yu et al., 2003)  |
| <b>Clozapine</b>     | CYP2D6               | <i>poor metabolizer</i>                                      | Hiperglikemia (Vasudev et al., 2017)   |
| <b>Codeine</b>       | CYP2D6               | <i>ultra-rapid metabolizer</i>                               | <i>dizziness</i> atau sakit kepala ringan, mual, muntah, mulut kering, pandangan kabur, gatal, ruam (Prows et al., 2014)<br><sup>a</sup> Depresi napas dan susunan saraf pusat (Ginsberg, 2005; Madadi et al., 2007) |
| <b>Efavirenz</b>     | CYP2B6               | <i>poor metabolizer</i>                                      | Hepatotoksik (Manosuthi et al., 2014)  |
| <b>Fluorouracil</b>  | DPYD                 | <i>intermediate</i> atau <i>poor metabolizer</i>             | Toksisitas gastrointestinal, hematologi, dan <i>hand-foot syndrome</i> (Jeong et al., 2021)  |
| <b>Gefitinib</b>     | CYP2D6               | <i>poor metabolizer</i>                                      | Ruam (Suzumura et al., 2012)   |



|  |                      |   |  |
|--|----------------------|---|--|
|  |                      |   | <sup>b</sup> Hepatotoksik (Takimoto et al., 2013)  |
| <b>Irinotecan</b>                        | UGT1A1               | *28/*28 ( <i>poor metabolizer</i> )   | Diare, neutropeni (Hirasawa et al., 2013; C. Xu et al., 2016)  |
| <b>Isoniazid</b>                         | NAT                  | <i>poor metabolizer</i>   | Hepatotoksik (Huang et al., 2002; Sotsuka et al., 2011)  |
| <b>Lapatinib</b>                         | HLA-DRB1<br>HLA-DQA1 | *07:01 alel positif<br>*02:01 alel positif                                      | Hepatotoksik (Parham et al., 2016)   |
| <b>Metoclopramide</b>                    | CYP2D6               | <i>poor metabolizer</i>   | <i>Acute dystonic reaction</i> (Sindrom Ekstrapiramidal) (van der Padt et al., 2006; Wee Chua et al., 2019)  |
| <b>Nilotinib</b>                         | UGT1A1               | *28/*28 ( <i>poor metabolizer</i> )   | Hiperbilirubinemia (Shibata et al., 2014)  |
| <b>Oxcarbazepine</b>                     | HLA-B                | *15:02 alel positif   | <i>Drug reaction with eosinophilia and systemic symptoms</i> (DRESS), SSJ (Liu et al., 2018)                 |
| <b>Pazopanib</b>                         | HLA-B;<br>UGT1A1     | HLA-B: *57:01 alel positif<br>UGT1A1: *28/*28 ( <i>poor metabolizer</i> )       | Hepatotoksik (C. F. Xu et al., 2016)<br><br>Hiperbilirubinemia (Xu et al., 2010)                             |
| <b>Propafenone</b>                       | CYP2D6               | <i>poor metabolizer</i>   | Efek samping sistem saraf pusat (pandangan kabur, <i>dizziness</i> , dan parastesia) (Siddoway et al., 1987) |
| <b>Simvastatin</b>                       | SLCO1B1              | 521 TC or 521 CC ( <i>intermediate</i> atau <i>poor function transporters</i> ) | Miopati (Jiang et al., 2016)   |
| <b>Sulfamethoxazole and Trimethoprim</b> | NAT                  | <i>poor metabolizer</i>   | Hepatotoksik (Soejima et al., 2007)<br>Reaksi hipersensitivitas (Zielin, 1998)                               |
| <b>Sulfasalazine</b>                     | NAT                  | <i>poor metabolizer</i>   | Reaksi hipersensitivitas (Chen et al., 2007; Tanaka et al., 2002)  |



|                    |                           |  |   |
|--------------------|---------------------------|--|---|
| <b>Tolterodine</b> | CYP2D6                    | <i>poor metabolizer</i>                                  | <sup>a</sup> Pemanjangan interval QT (Lui and Fung, 2010)                               |
| <b>Tramadol</b>    | CYP2D6                    | <i>ultra-rapid metabolizer</i>                           | Mual, muntah (Siew et al., 2007)<br><sup>a</sup> Depresi napas (Orliaguet et al., 2015) |
| <b>Warfarin</b>    | CYP2C9 dan VKORC1-1639G>A | CYP2C9: <i>intermediate</i> atau <i>poor metabolizer</i> | Perdarahan (Misasi et al., 2016; Nahar et al., 2013)                                    |

<sup>a</sup>Case Report

<sup>b</sup>Digunakan bersama inhibitor CYP3A4

**Tabel 3.** Obat-Obat dengan Potensi Efek Subterapeutik yang Beredar di Indonesia dan Rekomendasi Penggunaan Obat Sesuai Pendekatan Farmakogenomik

| Obat              | Gen     | Fenotip (referensi dan rekomendasi dosis)        | Rekomendasi  |
|-------------------|---------|--|--|
| Clopidogrel       | CYP2C19 | <i>intermediate</i> atau <i>poor metabolizer</i> | Hindari penggunaan clopidogrel (Dean and Kane, 2022) |
| Codein            | CYP2D6  | <i>poor metabolizer</i>                          | Hindari penggunaan opioid (Dean and Kane, 2021)      |
| <b>Tacrolimus</b> | CYP3A5  | <i>intermediate metabolizer</i>                  | Penyesuaian dosis sesuai kadar obat (PharmKGB, 2023) |

### Faktor Lain Yang Mempengaruhi Respon Obat

Hubungan antara dosis, konsentrasi obat, dan efek obat dapat dipengaruhi oleh faktor fisiologis maupun patologis (Brunton et al., 2017; Katzung, 2018). Kadar suatu obat di dalam tubuh akan dipengaruhi oleh kemampuan obat tersebut diabsorpsi oleh tubuh. Perubahan pH saluran cerna dapat menyebabkan perubahan kapasitas absorpsi suatu obat, yang mana dapat menyebabkan perubahan respon obat baik peningkatan kadar maupun

penurunan kadar obat tersebut (Brunton et al., 2017). Keadaan protein plasma juga mempengaruhi efek obat. Pada obat-obat yang memiliki ikatan protein tinggi dan rentang kadar terapeutik yang sempit, pergeseran sedikit saja pada ikatan obat dari protein plasma akan menyebabkan peningkatan kadar obat yang bermakna sehingga meningkatkan potensi terjadinya efek samping (Katzung, 2018). Keadaan hipoalbuminemia yang berat juga dapat meningkatkan potensi efek samping obat yang berikatan dengan



albumin (Lee et al., 2016). Ikatan obat-albumin merupakan bentuk inaktif, sedangkan obat yang dapat memberikan respon farmakologi adalah yang obat bebas (Brunton et al., 2017). Penurunan fungsi ginjal juga dapat berkontribusi terhadap peningkatan potensi toksisitas obat-obat yang diekskresikan melalui ginjal. Apabila terjadi penurunan fungsi ginjal, maka eliminasi obat pun mengalami penurunan. Sehingga, terjadi peningkatan risiko toksisitas obat (Lea-Henry et al., 2018). Di sisi lain perbedaan atau perubahan fisiologis pada anak-anak, ibu hamil, geriatri, dan penyakit kritis dapat mempengaruhi respon obat (Katzung, 2018). Efek samping akibat obat juga dapat disebabkan oleh faktor lain seperti interaksi antar obat, interaksi obat dan makanan, serta eksipien obat (de Boer et al., 2015; Moore et al., 2015; Shah, 2014).

## KESIMPULAN

Farmakogenomik merupakan salah satu modalitas baru dalam pendekatan farmakologi. Pendekatan secara farmakogenomik dapat membantu menurunkan risiko terjadinya efek samping dan mengoptimalkan efektivitas obat, sehingga menjadikan pengobatan lebih presisi. Namun, efek suatu obat tidak hanya dipengaruhi oleh variasi genetik melainkan juga oleh banyak faktor seperti perubahan fisiologis, keadaan patologis, serta efek lainnya. Faktor-faktor tersebut perlu

dipertimbangkan oleh klinisi dalam pemberian terapi.

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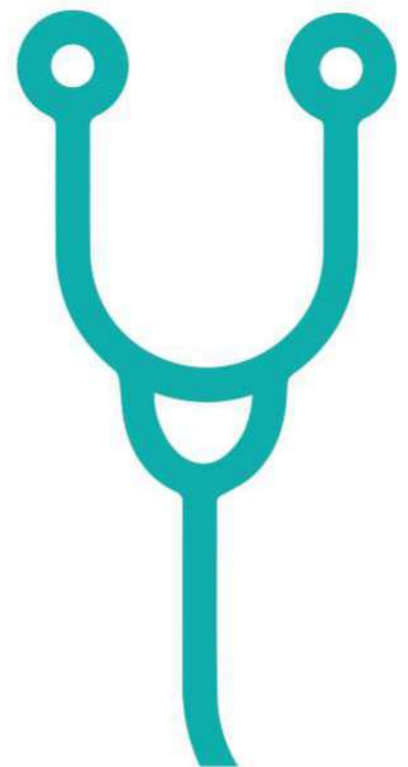
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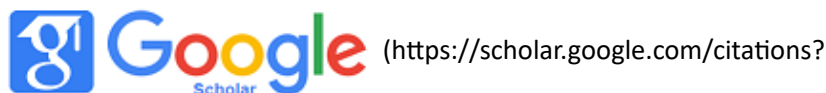
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