Statistical learning for complex data to enable precision medicine strategies

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Chapter 8

General discussion and summary

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Explaining treatment response variability between and within patients can support treatment and dosing optimization, to improve treatment of individual patients. This thesis discussed multiple aspects of treatment variability and the associated statistical learning techniques which can be used to explain and/or predict part of that variability. Even though in recent times the availability of several high-throughput measurement technologies has created many new opportunities to develop improved treatment strategies, deriving actionable insights from such data remains a challenge (Section I). To this end, the use of longitudinal and high-dimensional data analysis techniques is needed to explore omics data for explaining treatment response and clinical course (Section II), and to answer clinical questions from routine healthcare data from hospitals and research institutes (Section III).

8.1 Data science in pharmaceutical research

To gain knowledge about the treatment response, clinical trials are a golden standard, but not all factors and not all patient populations can be included in clinical trials. Inclusion of data collected as part of routine health check-ups or from wearables and home devices could improve treatment decision making (Morrato et al., 2007; Swift et al., 2018). In Chapter 2, we described the additional types of data that could facilitate clinical decision making, through placebo-responder prediction, endpoint and biomarker discovery and prognosis and drug response prediction, and which opportunities and pitfalls these data introduce. We focused on pediatric patients, due to the difficulties in recruiting patients and the large individual variability, which call for research complementary to clinical trials (Brussee et al., 2016).

Real world data cannot be analyzed in the same way as classical clinical trial data, which calls for adaptation or extension of statistical methods used for pharmacological research. Machine learning methods, mostly statistical learning techniques, are considered for these types of data. This poses an additional challenge, because an important part of clinical studies is the interpretability of methods used, due to the need to be able to explain the choice of clinical decisions (Knoppers & Thorogood, 2017).

8.2 High-dimensional biomarker discovery

Due to the developments in biochemical measurement techniques, the molecular make-up of a human can be measured, for example in serum blood samples. Data about molecules such as metabolites, RNA and DNA, generally referred to collectively as ‘omics’ data, can nowadays be measured, greatly increasing the precision with which patients can be described (Pearson, 2016). Although these omics data give abundantly more measurements, discovery of influential or predictive biomarkers (Depledge et al., 1993) from omics data adds a number of data analysis challenges,

especially in the case of studying changes over time. Working with both longitudinal and high-dimensional data makes current available methods that often focus on only one of the two, hard to use directly.

In Chapter 3, we identified biomarkers from high-dimensional genomics data for the tumor treatment response in patient-derived xenografts, using a novel two-step approach (Zwep, Haakman, et al., 2021). The data were retrieved from published research (Gao et al., 2015), where the tumor growth of mice models was measured over time, and genomic data, in the form of copy number variations (CNV's), were measured at baseline. In the first step, we used a mathematical tumor growth inhibition model to describe the longitudinal tumor growth curves. This model characterizes a tumor growth curve with three parameters: the tumor growth (k_g), the drug effect (k_d) and the drug resistance development (k_r). These parameters were estimated based on the data, on which both a population effect and the individual effects (empirical Bayes estimates) were estimated. The individual parameter estimates were used in a second step, as outcomes in lasso regression, where they were related to the high-dimensional genomic data. Using cross-validation, we found a 4% median decrease in prediction error, by including genomic data. We were able to detect genomic effects on a pathway level, by using a pathway-informed group-lasso.

High-dimensional data pose a challenge, due to easily overfitting on the data. Although tumor growth inhibition models are readily available, pharmacometric estimation techniques currently are not able to estimate high-dimensional covariate effects for prediction and using the proposed two-step approach circumvents the computational difficulty. A two-step approach can, however, cause inflated errors: if error is introduced in the first step, this erroneous estimate is used in the second step. So assessing errors in both steps is important to reduce this risk.

In Chapter 4, longitudinal metabolomics data were studied to explore potential biomarkers for clinical course, the combination of treatment response and disease development, in hospitalized patients with community acquired pneumonia (CAP). We applied dimension reduction through principal component analysis, to explore patterns of metabolites over time and how different biochemical classes of metabolites relate to the clinical course. We calculated correlations between metabolites and two measures of clinical course: the CURB score, a score indicating how sick the patient is when entering the hospital, and the length of stay in the hospital, indicating how much time the patient took to recover. Metabolite patterns clearly changed over time within the patients, showing how important studying longitudinal metabolomics data in patients with CAP is. Several biochemical classes were identified that were correlated to the clinical course, such as the triglyceride and the lysophosphatidylcholine classes.

8.2.1 A path towards omics-related treatment individualization

Characterizing patients on a molecular level can potentially improve understanding of different treatment response and clinical course. However, these type of high-dimensional data pose a challenge in data analysis. The problem of sparsity in high-

dimensional data can be tackled using different statistical methods. Pharmacometrics was also developed to deal with sparsity, in terms of number of patients and time points, to study dose response in sparse data (Pillai et al., 2005). In Chapter 3 we utilized pathway knowledge to reduce the dimension of possible solutions, by penalizing on a pathway level. Utilizing prior knowledge, such as understanding of dose response curves, or in the present case, relations among genes, can reduce the dimensions that are irrelevant for the research question (van Nee et al., 2021).

Many omics technologies are currently shown to be promising, but most are not used in practice for the individualization of drug treatment. The development of metabolomics measurement technology allows for a very low-level characterization of the patient's physiological processes (Beger et al., 2016). However, both the measurement of metabolites and the high variability of concentrations, make it hard to distinguish between-individual variance from within-individual variance. In Chapter 4, we address this issue by analyzing changes over time, instead of measurements at one time point.

8.3 Real world data

Routine healthcare data are often to monitor patients and their treatment response, and a growing part of these data are stored and accessible for researchers. These real world data can improve our understanding of topics in pharmaceutical science.

Antibiotic resistance poses a threat to global health. How big of a threat and how it is developing is continuously monitored through surveillance of antibiotic resistance in hospitals (van der Kuil et al., 2017). Due to increased monitoring of antibiotic resistance, minimal inhibitory concentrations (MIC) of clinical bacterial strains are often measured, which could be used for detection of collateral sensitivity (CS). CS occurs when one drug can reduce resistance against a second drug, and could be useful in combatting or overcoming infections with resistant pathogens (Aulin et al., 2021). Although the phenomenon has been detected in the lab, knowledge of its prevalence in clinical practice is currently very limited.

In Chapter 5, we proposed a method for quantification of collateral effects in routine healthcare MIC data (Zwep, Haakman, et al., 2021). The proposed log2 fold change is an interpretable measure also used in experimental research, allowing easy comparison between experimental and observational results and enabling directionality between two antibiotics. This measure was used in Chapter 6 to quantify CS in large MIC data from different data sources, indicating CS is occurring in clinical practice, but it is very hard to find specific patterns over different antibiotic classes or species, and this lack of generalizability makes it hard to use collateral sensitivity in clinical studies and in practice (Nichol et al., 2019).

Next to healthcare data on pathogens, patient-level data are also collected during routine patient care. These data contain different types of covariates, such as biomarker concentrations, demographics, and other patient characteristics (Currie & MacDonald, 2000). In pharmacometric modeling, these characteristics are often used

to explain and predict inter-patient variability in pharmacokinetics and pharmacodynamics, with the possibility to extent to special patient populations. Pharmacometric simulations require the simulation of these patient covariates, but sharing these sensitive patient data between hospitals and research groups is often difficult, due to the protection of the patients' privacy.

In Chapter 7, we proposed the use of copulas as a suitable method for virtual patient simulation. Copulas are multivariate distribution functions that can capture joint distributions and provide a flexible way to describe and simulate patient covariate sets from these densities. Most covariates are not independent of each other, so modeling this dependency adequately is required for the simulation of realistic virtual patients and a joint distribution function captures this dependency between different covariates. Our study showed copulas are able to simulate realistic patient populations using copulas (Zwep et al., 2022). Realistic virtual patients are required to simulate different patient populations, enabling extrapolation of found results to specific patient populations of interest.

The copulas need to be estimated on the basis of data that are not always available to researchers. However, data collected by hospitals and research institutes can be used to estimate the copulas and these copulas can be shared with researchers to enable studying the population, without granting access to the underlying patient level data. This way, covariates of patient populations can be shared between researchers and hospitals, without concern about the privacy of the patients.

8.4 Perspectives and conclusions

8.4.1 Integration of statistics and pharmacometrics

Pharmacometrics and statistics, although two very related fields, have developed separately throughout large parts of their history. Pharmacokinetic and pharmacodynamic models are based on concentration and effect over time profiles, respectively. Development and studies of these models generally require knowledge about or data of concentrations, system-parameters and drug-specific parameters. Modeling is usually done using nonlinear mixed effect models, a statistical framework, very common in pharmacometrics, but not in many other fields of statistics, where (generalized) linear mixed effect models are more commonly used (McCulloch & Searle, 2000; Pillai et al., 2005).

Nonlinear mixed effect models are very useful for describing the usually nonlinear relations between time and drug concentrations and/or effects. They offer a solution to the longitudinal and unbalanced nature of the data to estimate parameter values and predict treatment responses (Pillai et al., 2005). Recently, the inclusion of high-dimensional data as potential explanatory variables in pharmacometric research has compelled the pharmacometrics community to involve other statistical methods, which are able to deal with this high-dimensionality.

Next to statistical learning methods for high-dimensional data analysis, such as

regularization methods and dimension reduction, artificial intelligence methods, such as (deep) neural networks, have recently gained a lot of popularity in pharmacometrics (Chaturvedula et al., 2019; Janssen et al., 2022; McComb et al., 2021). However, actual implementation of both statistical learning and artificial intelligence approaches remains a challenge (Knights & Ramanathan, 2016).

In this thesis we proposed a two-step method for identifying high-dimensional biomarkers in a tumor growth model, showing how to incorporate nonlinear mixed effect models with the lasso method (Zwep, Duisters, et al., 2021). Next to this combination of pharmacometrics and statistics, we also explored the use of copulas to facilitate virtual patient covariate sets. Both projects aimed to improve current pharmacometric practices. The goal is not to implement new methods of data science, the goal is to better predict clinical outcomes and to be able to optimize treatments. Integrating statistical methods and pharmacometrics is not a goal on its own, although it sometimes seems to be treated that way, introducing and using overcomplicated machine learning methods, while other techniques are readily available (Volovici et al., 2022).

Although integration of statistics and pharmacometrics is a natural way of expanding the types of research and data analysis possible, to improve treatment optimization, more research is needed to find the ways of integrating these two, while keeping the end goal in mind. (van der Kuil et al., 2017)

8.4.2 The importance of interpretability in pharmacology

When data and data analysis become more complex, sometimes interpreting predictions, metrics and underlying parameter values also increases in complexity. This affects the way science is conducted in different ways: in terms of effect size interpretation, understanding of clinical decision making, and biological understanding of the system.

Interpretable measures, such as the collateral sensitivity measure proposed in Chapter 5, facilitate the translation between experimental results and clinical observations, and can help to understand clinical relevance through interpreting the effect size (Zwep, Haakman, et al., 2021).

In Chapter 2, we briefly discussed the importance of interpretable clinical decision making, due to the need for physicians to understand the reasoning behind their decisions (Goulooze et al., 2020). Understanding the underlying decision making process of clinical advise is important for healthcare professionals to understand whether they should follow the advice, or treat differently in a specific case. An emerging field concerned with this problem is explainable artificial intelligence, where 'black box algorithms', models without interpretable model and parameter values, are extended with a method to show what the predictions are based on (Doshi-Velez & Kim, 2018; Xu et al., 2019). However, current discussions are going on about the usefulness of these explanations in individual clinical decisions, deeming current techniques unviable for clinical decision making (Ghassemi et al., 2021).

Interpretability can facilitate in the understanding of the underlying biological sys-

tems. By understanding which factors and processes drive a treatment or disease effect, it is possible to study new drugs. Especially omics research focusses on describing the biological system on a molecular level, to track changes causing or caused by the disease in order to counteract them (Perakakis et al., 2018). Biological understanding can be improved by studying sets of molecules, but can also be retrieved through looking at biological pathways or biochemical classes of molecules, giving a more high-level understanding of the biological processes.

Improved biological understanding allows more accurate modeling of biological systems, which is what is done in translational pharmacometrics through physiological understanding of the processes in drug responses. If a model captures the physiological processes well, it becomes possible to extrapolate predictions to new medication or populations (Agoram et al., 2007; Musante et al., 2016; Pérez-Nueno, 2015).

8.4.3 Generalizing results

Knowledge of mechanisms and patient responses becomes useful if the results of a study can be generalized outside the region of the data analyzed. In first instance, exploratory research is needed to obtain insight in which variables might be of importance for treatment responses, such as the metabolites that might be of interest for the clinical course in longitudinal CAP patients (Chapter 4). However, generalization requires a different framework (Leek & Peng, 2015). Two distinct aims for generalization have been formulated in Chapter 3: the understanding of biological mechanisms contributing to variable treatment responses and the prediction of tumor growth inhibition for different treatments. These two aims can more generally be described as inference and prediction respectively, and are not fully separable in terms of research aims (Bzdok & Ioannidis, 2019).

In inference, the effect size is of interest, for example the correlation between variables or the difference between groups. Inference includes methods of parameter estimation and hypothesis testing to quantify effects and test whether these effects are expected to be 'real'. By having a model of the world that captures the underlying data generating process, it is possible to infer a mechanism in a more general population, such as the effect of a treatment on a clinical outcome (Bzdok & Ioannidis, 2019). Hypothesis testing is based on this principle. With the increase of complexity and size of data(sets), more variables and correlations are of interest at once. Evaluating the generalizability of the found results requires an extra step in hypothesis testing. In Chapter 5 and Chapter 6, we evaluated large numbers of tests, by estimating and testing all combinations of antibiotics. By using a multiple testing correction, we controlled the probability of false hypothesis rejections.

Prediction is another aim in research, where not the effect size, but a specific patient response is of interest. Generalizability is ensured in prediction by validation, through comparison between observed values and predicted values in a sample that has not been used to make the underlying prediction. In prediction, the high-dimensional setting often causes overfitting, being able to predict the outcomes for the data that produced the underlying model really well, but not being able to predict

newly observed data. In Chapter 3, lasso regression was used both for inference and prediction (Tibshirani, 1996). The lasso uses a hyperparameter to determine shrinkage, which can be tuned through cross-validation, to reduce the risk of overfitting.

Despite the use of multiple testing correction or cross-validation based hyperparameter tuning, validation is important to the progress of science in both estimation of treatment effects and prediction of patient's individual treatment responses (Ghosh & Poisson, 2009). The research cycle of pharmacometrics is based on this principle, by modeling pharmacological processes, based on previous knowledge and data, and validating the predictive performance with new data. When the pharmacological model is established, it can be used for patient predictions and even population extrapolation (Marshall et al., 2016).

In the field of precision medicine and - more specifically - omics research, generalization is hard to achieve, because of the increased dimensionality and the explorative nature of omics research. It is important to involve experts and robust data analysis strategies to avoid overfitting and to gain a good understanding of pharmacology and biology (Buyse et al., 2010; Wilkinson et al., 2020).

8.4.4 Data sharing opportunities

The adaptation of statistical tools often relies on the use of available data sources, which our research on biomarkers for tumor growth inhibition (Chapter 3) and collateral sensitivity (Chapter 5, Chapter 6) is also based on. There is a call to increase data sharing to improve and accelerate research (Hulsen, 2020). Data sharing is a particularly difficult topic within healthcare, due to the intricate privacy issues and the laws protecting privacy rights (Knoppers & Thorogood, 2017). Developing ways to share data, while preserving privacy is an active field of research (Bonomi et al., 2020; Sweeney, 2002). One way to share information, is by sharing summary measures of cohorts, instead of the patient level data. In Chapter 7, we proposed to do this by using copulas to share information on a population level, while preserving the privacy of individual patients (Gambs et al., 2021). More data sharing can support precision medicine develop, but these data should be handled with caution, and methods like the copula could support this aim.

8.5 Conclusions

The use of statistical learning methods in precision medicine supports unraveling treatment resonse variability, using different types of data, such as high-dimensional omics data, but also routine healthcare data. Integration of statistical learning methods facilitates further pharmacological research, but care needs to be taken to keep a clear pharmacological interpretation of the results.

References

Agoram, B. M., Martin, S. W., & van der Graaf, P. H. (2007, Dec). The role of mechanism-based pharmacokinetic–pharmacodynamic (PK–PD) modelling in translational research of biologics. *Drug Discovery Today*, *12*(23-24), 1018–1024. Retrieved from https://doi.org/10.1016%2Fj.drudis.2007.10.002 doi: 10.1016/j.drudis.2007.10.002

Aulin, L. B. S., Liakopoulos, A., van der Graaf, P. H., Rozen, D. E., & van Hasselt, J. G. C. (2021, Sep). Design principles of collateral sensitivity-based dosing strategies. *Nature Communications*, *12*(1). Retrieved from https://doi.org/10.1038%2Fs41467-021-25927-3 doi: 10.1038/s41467-021-25927-3

Beger, R. D., Dunn, W., Schmidt, M. A., Gross, S. S., Kirwan, J. A., Cascante, M., ... Kaddurah-Daouk, R. (2016, Sep). Metabolomics enables precision medicine: "A White Paper, Community Perspective". *Metabolomics*, *12*(9), 149. Retrieved from http://link.springer.com/10.1007/s11306-016-1094-6 doi: 10.1007/s11306-016-1094-6

Bonomi, L., Huang, Y., & Ohno-Machado, L. (2020, Jun). Privacy challenges and research opportunities for genomic data sharing. *Nature Genetics*, *52*(7), 646–654. Retrieved from https://doi.org/10.1038%2Fs41588-020-0651-0 doi: 10.1038/s41588-020-0651-0

Brussee, J. M., Calvier, E. A. M., Krekels, E. H. J., Välitalo, P. A. J., Tibboel, D., Allegaert, K., & Knibbe, C. A. J. (2016, Jun). Children in clinical trials: towards evidence-based pediatric pharmacotherapy using pharmacokinetic-pharmacodynamic modeling. *Expert Review of Clinical Pharmacology*, *9*(9), 1235–1244. Retrieved from https://doi.org/10.1080%2F17512433.2016.1198256 doi: 10.1080/17512433.2016.1198256

Buyse, M., Sargent, D. J., Grothey, A., Matheson, A., & de Gramont, A. (2010, Apr). Biomarkers and surrogate end points—the challenge of statistical validation. *Nature Reviews Clinical Oncology*, *7*(6), 309–317. Retrieved from https://doi.org/10.1038%2Fnrclinonc.2010.43 doi: 10.1038/nrclinonc.2010.43

Bzdok, D., & Ioannidis, J. P. (2019, Apr). Exploration, inference, and prediction in neuroscience and biomedicine. *Trends in Neurosciences*, *42*(4), 251–262. Retrieved from https://doi.org/10.1016%2Fj.tins.2019.02.001 doi: 10.1016/j.tins.2019.02.001

Chaturvedula, A., Calad-Thomson, S., Liu, C., Sale, M., Gattu, N., & Goyal, N. (2019, Jun). Artificial intelligence and pharmacometrics: Time to embrace, capitalize, and advance? *CPT: Pharmacometrics & Systems Pharmacology*, *8*(7), 440–443. Retrieved from https://doi.org/10.1002%2Fpsp4.12418 doi: 10.1002/psp4.12418

Currie, C. J., & MacDonald, T. M. (2000). Use of routine healthcare data in safe and cost-effective drug use. *Drug Safety*, *22*(2), 97–102. Retrieved from https://doi.org/10.2165%2F00002018-200022020-00002 doi: 10.2165/00002018-200022020-00002

Depledge, M. H., Amaral-Mendes, J. J., Daniel, B., Halbrook, R. S., Kloepper-Sams, P., Moore, M. N., & Peakall, D. B. (1993). The conceptual basis of the biomarker approach. In *Biomarkers* (pp. 15–29). Springer Berlin Heidelberg. Retrieved from https://doi.org/10.1007%2F978-3-642-84631-1_2 doi: 10.1007/978-3-642-84631-1_2

Doshi-Velez, F., & Kim, B. (2018). Considerations for evaluation and generalization in interpretable machine learning. In *The springer series on challenges in machine learning* (pp. 3–17). Springer International Publishing. Retrieved from https://doi.org/10.1007%2F978-3-319-98131-4_1 doi: 10.1007/978-3-319-98131-4_1

Gambs, S., Ladouceur, F., Laurent, A., & Roy-Gaumond, A. (2021, Apr). Growing synthetic data through differentially-private vine copulas. *Proceedings on Privacy Enhancing Technologies*, *2021*(3), 122–141. Retrieved from https://doi.org/10.2478%2Fpopets-2021-0040 doi: 10.2478/popets-2021-0040

Gao, H., Korn, J. M., Ferretti, S., Monahan, J. E., Wang, Y., Singh, M., ... Sellers, W. R. (2015, Oct). High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nature Medicine*, *21*(11), 1318–1325. Retrieved from https://doi.org/10.1038%2Fnm.3954 doi: 10.1038/nm.3954

Ghassemi, M., Oakden-Rayner, L., & Beam, A. L. (2021, Nov). The false hope of current approaches to explainable artificial intelligence in health care. *The Lancet Digital Health*, *3*(11), e745–e750. Retrieved from https://doi.org/10.1016%2Fs2589-7500%2821%2900208-9 doi: 10.1016/s2589-7500(21)00208-9

Ghosh, D., & Poisson, L. M. (2009, Jan). "omics" data and levels of evidence for biomarker discovery. *Genomics*, *93*(1), 13–16. Retrieved from https://doi.org/10.1016%2Fj.ygeno.2008.07.006 doi: 10.1016/j.ygeno.2008.07.006

Goulooze, S. C., Zwep, L. B., Vogt, J. E., Krekels, E. H., Hankemeier, T., Anker, J. N., & Knibbe, C. A. (2020, Apr). Beyond the Randomized Clinical Trial: Innovative Data Science to Close the Pediatric Evidence Gap.

Clinical Pharmacology & Therapeutics, *107*(4), 786–795. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1744https://onlinelibrary.wiley.com/doi/10.1002/cpt.1744 doi: 10.1002/cpt.1744

Hulsen, T. (2020, Apr). Sharing is caring—data sharing initiatives in healthcare. *International Journal of Environmental Research and Public Health*, *17*(9), 3046. Retrieved from https://doi.org/10.3390%2Fijerph17093046 doi: 10.3390/ijerph17093046

Janssen, A., Bennis, F. C., & Mathôt, R. A. A. (2022, Aug). Adoption of machine learning in pharmacometrics: An overview of recent implementations and their considerations. *Pharmaceutics*, *14*(9), 1814. Retrieved from https://doi.org/10.3390%2Fpharmaceutics14091814 doi: 10.3390/pharmaceutics14091814

Knights, J., & Ramanathan, M. (2016). Detecting pharmacokinetic and pharmacodynamic covariates from high-dimensional data. In *Systems pharmacology and pharmacodynamics* (pp. 277–301). Springer International Publishing. Retrieved from https://doi.org/10.1007%2F978-3-319-44534-2_13 doi: 10.1007/978-3-319-44534-2_13

Knoppers, B. M., & Thorogood, A. M. (2017, Aug). Ethics and big data in health. *Current Opinion in Systems Biology*, *4*, 53–57. Retrieved from https://doi.org/10.1016%2Fj.coisb.2017.07.001 doi: 10.1016/j.coisb.2017.07.001

Leek, J. T., & Peng, R. D. (2015, Mar). What is the question? *Science*, *347*(6228), 1314–1315. Retrieved from https://doi.org/10.1126%2Fscience.aaa6146 doi: 10.1126/science.aaa6146

Marshall, S., Burghaus, R., Cosson, V., Cheung, S., Chenel, M., DellaPasqua, O., ... Visser, S. (2016, Mar). Good practices in model-informed drug discovery and development: Practice, application, and documentation. *CPT: Pharmacometrics & Systems Pharmacology*, *5*(3), 93–122. Retrieved from https://doi.org/10.1002%2Fpsp4.12049 doi: 10.1002/psp4.12049

McComb, M., Bies, R., & Ramanathan, M. (2021, Mar). Machine learning in pharmacometrics: Opportunities and challenges. *British Journal of Clinical Pharmacology*, *88*(4), 1482–1499. Retrieved from https://doi.org/10.1111%2Fbcp.14801 doi: 10.1111/bcp.14801

McCulloch, C. E., & Searle, S. R. (2000). *Generalized, linear, and mixed models*. Wiley. Retrieved from https://doi.org/10.1002%2F0471722073 doi: 10.1002/0471722073

Morrato, E. H., Elias, M., & Gericke, C. A. (2007, Dec). Using population-based routine data for evidence-based health policy decisions: lessons from three examples of setting and evaluating national health policy in australia, the UK and the USA. *Journal of Public Health*, *29*(4), 463–471. Retrieved from https://doi.org/10.1093%2Fpubmed%2Ffdm065 doi: 10.1093/pubmed/fdm065

Musante, C., Ramanujan, S., Schmidt, B., Ghobrial, O., Lu, J., & Heatherington, A. (2016, Nov). Quantitative systems pharmacology: A case for disease models. *Clinical Pharmacology & Therapeutics*, *101*(1), 24–27. Retrieved from https://doi.org/10.1002%2Fcpt.528 doi: 10.1002/cpt.528

Nichol, D., Rutter, J., Bryant, C., Hujer, A. M., Lek, S., Adams, M. D., ... Scott, J. G. (2019, Jan). Antibiotic collateral sensitivity is contingent on the repeatability of evolution. *Nature Communications*, *10*(1). Retrieved from https://doi.org/10.1038%2Fs41467-018-08098-6 doi: 10.1038/s41467-018-08098-6

Pearson, E. R. (2016, May). Personalized medicine in diabetes: the role of 'omics' and biomarkers. *Diabetic Medicine*, *33*(6), 712–717. Retrieved from https://doi.org/10.1111%2Fdme.13075 doi: 10.1111/dme.13075

Perakakis, N., Yazdani, A., Karniadakis, G. E., & Mantzoros, C. (2018, Oct). Omics, big data and machine learning as tools to propel understanding of biological mechanisms and to discover novel diagnostics and therapeutics. *Metabolism*, *87*, A1–A9. Retrieved from https://doi.org/10.1016%2Fj.metabol.2018.08.002 doi: 10.1016/j.metabol.2018.08.002

Pérez-Nueno, V. I. (2015, Aug). Using quantitative systems pharmacology for novel drug discovery. *Expert Opinion on Drug Discovery*, *10*(12), 1315–1331. Retrieved from https://doi.org/10.1517%2F17460441.2015.1082543 doi: 10.1517/17460441.2015.1082543

Pillai, G. C., Mentré, F., & Steimer, J.-L. (2005, Apr). Non-linear mixed effects modeling – from methodology and software development to driving implementation in drug development science. *Journal of Pharmacokinetics and Pharmacodynamics*, *32*(2), 161–183. Retrieved from https://doi.org/10.1007%2Fs10928-005-0062-y doi: 10.1007/s10928-005-0062-y

Sweeney, L. (2002, Oct). k-Anonymity: a Model for Protecting Privacy. *International Journal of Uncertainty, Fuzziness and Knowledge-Based Systems*, *10*(05), 557–570. Retrieved from https://www.worldscientific.com/doi/abs/10.1142/S0218488502001648 doi: 10.1142/S0218488502001648

Swift, B., Jain, L., White, C., Chandrasekaran, V., Bhandari, A., Hughes, D. A., & Jadhav, P. R. (2018, May). Innovation at the intersection of clinical trials and real-world data science to advance patient care. *Clinical and Translational Science*, *11*(5), 450–460. Retrieved from https://doi.org/10.1111%2Fcts.12559 doi: 10.1111/cts.12559

Tibshirani, R. (1996). Regression Shrinkage and Selection via the Lasso. *Royal Statistical Society*, *58*(1), 267–288. Retrieved from www.jstor.org/stable/2346178

van der Kuil, W. A., Schoffelen, A. F., de Greeff, S. C., Thijsen, S. F., Alblas, H. J., Notermans, D. W., ... and, T. L. (2017, Nov). National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the netherlands. *Eurosurveillance*, *22*(46). Retrieved from https://doi.org/10.2807%2F1560-7917.es.2017.22.46.17-00062 doi: 10.2807/1560-7917.es.2017.22.46.17-00062

van Nee, M. M., Wessels, L. F., & van de Wiel, M. A. (2021, Aug). Flexible co-data learning for high-dimensional prediction. *Statistics in Medicine*, *40*(26), 5910–5925. Retrieved from https://doi.org/10.1002%2Fsim.9162 doi: 10.1002/sim.9162

Volovici, V., Syn, N. L., Ercole, A., Zhao, J. J., & Liu, N. (2022, Sep). Steps to avoid overuse and misuse of machine learning in clinical research. *Nature Medicine*, *28*(10), 1996–1999. Retrieved from https://doi.org/10.1038%2Fs41591-022-01961-6 doi: 10.1038/s41591-022-01961-6

Wilkinson, J., Arnold, K. F., Murray, E. J., van Smeden, M., Carr, K., Sippy, R., ... Tennant, P. W. G. (2020, Dec). Time to reality check the promises of machine learning-powered precision medicine. *The Lancet Digital Health*, *2*(12), e677–e680. Retrieved from https://doi.org/10.1016%2Fs2589-7500%2820%2930200-4 doi: 10.1016/s2589-7500(20)30200-4

Xu, F., Uszkoreit, H., Du, Y., Fan, W., Zhao, D., & Zhu, J. (2019). Explainable AI: A brief survey on history, research areas, approaches and challenges. In *Natural language processing and chinese computing* (pp. 563–574). Springer International Publishing. Retrieved from https://doi.org/10.1007%2F978-3-030-32236-6_51 doi: 10.1007/978-3-030-32236-6_51

Zwep, L. B., Duisters, K. L. W., Jansen, M., Guo, T., Meulman, J. J., Upadhyay, P. J., & Hasselt, J. G. C. (2021, Apr). Identification of high-dimensional omics-derived predictors for tumor growth dynamics using machine learning and pharmacometric modeling. *CPT: Pharmacometrics & Systems Pharmacology*, *10*(4), 350–361. Retrieved from https://doi.org/10.1002%2Fpsp4.12603 doi: 10.1002/psp4.12603

Zwep, L. B., Guo, T., Nagler, T., Knibbe, C. A., Meulman, J. J., & van Hasselt, J. C. (2022). Virtual patient simulation using copula modeling. *[in preparation]*.

Zwep, L. B., Haakman, Y., Duisters, K. L. W., Meulman, J. J., Liakopoulos, A., & van Hasselt, J. G. C. (2021, Sep). Identification of antibiotic collateral sensitivity and resistance interactions in population surveillance data. *JAC-Antimicrobial Resistance*, *3*(4). Retrieved from https://doi.org/10.1093%2Fjacamr%2Fdlab175 doi: 10.1093/jacamr/dlab175