Messages that are too exact

From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

1.1d Do not assume that it is possible to know who will benefit and who will be harmed.

Explanation

For some kinds of health problems, fair treatment comparisons can be made by giving different treatments to a patient at different times, and then comparing the outcomes associated with each of the different treatment periods. These are called n-of-1 trials because they compare the effects of alternative treatments in one patient *[Guyatt 1990 (SR)]*. For example, n-of-1 trials have compared paracetamol to non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis of the hip or knee *[Wegman 2003 (RS)]*. The results varied across patients. Most uncertainties about the effects of treatments cannot be compared in this way, however. For example, this person-specific approach cannot usually be used to compare a surgical treatment with a drug treatment.

Most treatment comparisons involve comparing similar groups of patients assigned to one among alternative treatments. Fair comparisons of treatments usually tell us what happened, on average, in groups of similar people. Usually, in a group of people who have used a treatment, some people benefit, some do not, and some may even be harmed. For example, the proportion of people who benefit from common pharmacological treatments varies from 1.5% – for aspirin to prevent serious vascular events (myocardial infarction, stroke, or vascular death) in people at high risk – to 58% – for proton pump inhibitors for relief of reflux oesophagitis *[Leucht 2015 (SR)]*. It is rarely possible to know in advance who will benefit from which treatment among alternatives, who will not benefit, or who will be harmed. Paradoxically, the only way to know whether "personalised medicine" – customising treatment for individuals – works is to test it in fair comparisons. Unless the customisation is 100% effective and 100% safe, it is still not possible to know in advance who will benefit from "personalised care" and who will not. Beyond n-of-1 trials, "personalised medicine" is not really personalised; it is simply an effort to identify subgroups of people who are most likely to benefit from specific treatments.

For example, HER2-positive breast cancer is when breast cancer cells have a protein receptor called HER2 (human epidermal growth factor receptor 2). About 20% of breast cancers are HER2-positive. Trastuzumab (Herceptin) and other monoclonal antibodies that block HER2 receptors to keep cancer cells from growing are used to treat HER2-positive breast cancer. So, those medicines are given to women with HER2-positive breast cancer and not to other women with breast cancer. However, not all women with HER2-positive breast cancer benefit from the medicine and some will experience serious harmful effects, such as congestive heart failure (CHF). For example, for women with breast cancer detected at an early stage who have a moderate risk of cancer recurrence or death in the next three years (30%) and a moderate risk of CHF (2%), only about 10% more women who take the medicine will benefit (experience disease-free survival) and about 8% more will be harmed (experience CHF) *[Moja 2012 (SR)]*. It is not possible to predict which among those women will benefit and which will be harmed.

Basis for this concept

"Personalised medicine" and "precision medicine" are sometimes used interchangeably. "Personalised medicine" is an older term. However, "personalised" may be misinterpreted to imply that treatments are developed uniquely for each individual *[National Research Council 2011]*. Although definitions of personalised and precision medicine vary, the aim is to improve decisions about treatments by using biological information and biomarkers to identify more precisely which (subgroups of) patients will benefit or which will be harmed by a treatment *[National Research Council 2011 , Schleidgen 2013 (SR)]*. This has the potential to increase the proportion of patients who benefit from a treatment or reduce the proportion who are harmed. Treatments very rarely have the same effect on everyone *[Glasziou 2007 , Leucht 2015 (SR), Nagendran 2016 (SR), Pereira 2012 (SR)]*. It will not be possible in the foreseeable future to know which individuals will benefit or which will be harmed within subgroups.

Observational, non-randomized studies, such as genetic association studies, can be used to develop hypotheses about new and clinically useful ways to group patients who may respond differently to a treatment. However, there are many ways to classify patients, and only some are useful. Moreover, most reported genetic associations, which could potentially be used to group people, are not reliable *[Dolan 2010 (SR), Ioannidis 2009 (SR), Köhler 2018 (SR)), Nair 2012 (SR), Richards 2009 (SR), Serghiou 2016 (SR), Staines-Urias 2012 (SR), Trifiletti 2017 (SR)]*. Therefore, the usefulness of grouping people based on genetic associations, or other factors, needs to be evaluated using randomized trials *[National Research Council 2011]*.

Personalised medicine has been portrayed as a revolution in health care *[Marcon 2018 (SR)]*. However, there is much uncertainty about the usefulness of most personalised medicine technologies *[Holmes 2009 (SR), Kasztura 2019 (SR), Plöthner 2016 (SR)]*.

Implications

Fair treatment comparisons provide the best basis for making well-informed decisions about treatments, but there is almost always some uncertainty about who will benefit, who will not, and who will be harmed.

References

Systematic reviews

Dolan SM, Hollegaard MV, Merialdi M, Betran AP, Allen T, Abelow C, et al. Synopsis of preterm birth genetic association studies: the preterm birth genetics knowledge base (PTBGene). Public Health Genomics. 2010;13(7-8):514-23. https://doi.org/10.1159/000294202

Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience. Ann Intern Med. 1990;112(4):293-9. https://doi.org/10.7326/0003-4819-112-4-293

Holmes MV, Shah T, Vickery C, Smeeth L, Hingorani AD, Casas JP. Fulfilling the promise of personalized medicine? Systematic review and field synopsis of pharmacogenetic studies. PLoS One. 2009;4(12):e7960. https://doi.org/10.1371/journal.pone.0007960

Ioannidis JP. Prediction of cardiovascular disease outcomes and established cardiovascular risk factors by genome-wide association markers. Circ Cardiovasc Genet. 2009;2(1):7-15. https://doi.org/10.1161/circgenetics.108.833392

Kasztura M, Richard A, Bempong NE, Loncar D, Flahault A. Cost-effectiveness of precision medicine: a scoping review. Int J Public Health. 2019;64(9):1261-71. https://doi.org/10.1007/s00038-019-01298-x

Köhler CA, Evangelou E, Stubbs B, Solmi M, Veronese N, Belbasis L, et al. Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. J Psychiatr Res. 2018;103:189-207. https://doi.org/10.1016/j.jpsychires.2018.05.020

Leucht S, Helfer B, Gartlehner G, Davis JM. How effective are common medications: a perspective based on meta-analyses of major drugs. BMC Med. 2015;13:253. https://doi.org/10.1186/s12916-015-0494-1
Marcon AR, Bieber M, Caulfield T. Representing a "revolution": how the popular press has portrayed personalized medicine. Genet Med. 2018;20(9):950-6. https://doi.org/10.1038/gim.2017.217
Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;2012(4):Cd006243. https://doi.org/10.1002/14651858.cd006243.pub2
Nagendran M, Pereira TV, Kiew G, Altman DG, Maruthappu M, Ioannidis JP, et al. Very large treatment effects in randomised trials as an empirical marker to indicate whether subsequent trials are necessary: meta-epidemiological assessment. BMJ. 2016;355:i5432. https://doi.org/10.1136/bmj.i5432
Nair VS, Maeda LS, Ioannidis JP. Clinical outcome prediction by microRNAs in human cancer: a systematic review. J Natl Cancer Inst. 2012;104(7):528-40. https://doi.org/10.1093/jnci/djs027
Pereira TV, Horwitz RI, Ioannidis JP. Empirical evaluation of very large treatment effects of medical interventions. JAMA. 2012;308(16):1676-84. https://doi.org/10.1001/jama.2012.13444
Plöthner M, Ribbentrop D, Hartman JP, Frank M. Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany. Adv Ther. 2016;33(9):1461-80. https://doi.org/10.1007/s12325-016-0376-8
Richards JB, Kavvoura FK, Rivadeneira F, Styrkársdóttir U, Estrada K, Halldórsson BV, et al. Collaborative meta-analysis: associations of 150 candidate genes with osteoporosis and osteoporotic fracture. Ann Intern Med. 2009;151(8):528-37. https://doi.org/10.7326/0003-4819-151-8-200910200-00006
Schleidgen S, Klingler C, Bertram T, Rogowski WH, Marckmann G. What is personalized medicine: sharpening a vague term based on a systematic literature review. BMC Med Ethics. 2013;14:55. https://doi.org/10.1186/1472-6939-14-55
Serghiou S, Kyriakopoulou A, Ioannidis JP. Long noncoding RNAs as novel predictors of survival in human cancer: a systematic review and meta-analysis. Mol Cancer. 2016;15(1):50. https://doi.org/10.1186/s12943-016-0535-1
Staines-Urias E, Paez MC, Doyle P, Dudbridge F, Serrano NC, Ioannidis JP, et al. Genetic association studies in pre-eclampsia: systematic meta-analyses and field synopsis. Int J Epidemiol. 2012;41(6):1764-75. https://doi.org/10.1093/ije/dys162
Trifiletti DM, Sturz VN, Showalter TN, Lobo JM. Towards decision-making using individualized risk estimates for personalized medicine: A systematic review of genomic classifiers of solid tumors. PLoS One. 2017;12(5):e0176388. https://doi.org/10.1371/journal.pone.0176388

Research studies

Wegman AC, van der Windt DA, de Haan M, Devillé WL, Fo CT, de Vries TP. Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis. Ann Rheum Dis. 2003;62(12):1156-61. https://doi.org/10.1136/ard.2002.002865

Other references

Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ. 2007;334(7589):349-51. https://doi.org/10.1136/bmj.39070.527986.68
National Research Council. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: National Academies Press; 2011.