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Incorporating financial toxicity considerations into clinical trial design to facilitate patient-centered decision-making in oncology

Running Head: Incorporating financial toxicity data

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Conflicts of Interest:

RJ has stock options as compensation for her advisory board role in Equity Quotient, a company that evaluates culture in health care companies; she has received personal fees from the NIH as a special government employee (in her role as a member of the Advisory Committee on Research on Women's Health and the Board of Scientific Counselors), the Greenwall Foundation, and the Doris Duke Charitable Foundation. She has received grants for unrelated work from the NIH, the Doris Duke Foundation, the Greenwall Foundation, the American Cancer Society, the Susan G. Komen Foundation, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium. She has a contract to conduct an investigator-initiated study with Genentech. She has served as an expert witness for Sherinian and Hasso, Dressman Benzinger LaVelle, and Kleinbard LLC. She is an uncompensated member of the NASEM's Committee on Women in Science, Engineering, and Medicine.

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Plain Language Summary:

Financial toxicity is increasingly recognized as an important and devastating consequence of cancer treatment that receives little attention when designing clinical trials. There is a significant

need to obtain this important information in the era of increasingly expensive anti-cancer treatments. Patients who are informed of all implications of therapy—efficacy, side effects, cost, and broader financial impact—are able to select the best cancer treatment for themselves.

Precis:

Despite understanding the prevalence and consequences of financial toxicity in breast cancer treatment, no robust mechanism exists to incorporate financial toxicity into patient-centered decision-making. Herein, we describe the need for prospective collection of financial toxicity outcomes in clinical trial design, with subsequent confirmation of impact by real-world evidence, and describe examples within oncology where perverse incentives have hindered the adoption or modification of therapies with potentially lower financial impact, such as minimal effective dosing of drug therapies or hypofractionation of radiotherapy.

Key words:

financial toxicity, clinical trial design, decision-making, supportive care, patient-centered

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Financial toxicity is increasingly recognized as an important and devastating consequence of cancer treatment[1] that receives little attention in prospective clinical trial design. Its prevalence is high, ranging from 20-60% depending on the specific cancer studied.[2, 3] In the past decade, we have learned much about financial toxicity. We can identify patients who may be at higher risk, including younger patients,[4] minoritized racial groups[5] and patients in lower socioeconomic strata.[6] Financial toxicity can cause patients to skip doses or not fill prescriptions altogether.[7] Financial toxicity directly impacts patients' quality of life,[8, 9] puts them at risk for bankruptcy,[10, 11] and may even increase mortality.[11] Methods to mitigate financial toxicity at the patient level exist but remain insufficient.[12]

Despite understanding the prevalence and consequences of this phenomenon, no robust mechanism exists to incorporate financial toxicity into patient-centered decision-making. Cancer patients are often expected to decide between treatment options solely on the basis of efficacy or insurance coverage. These decisions rarely incorporate information on how treatment options impact their ability to return to work and generate the income to pay for basic necessities or continue providing for dependents. Our current framework of evaluation of cancer therapies, driven by clinical trials and sometimes post-marketing surveillance studies, does not prospectively obtain financial toxicity-related information to allow for incorporation of the potential financial impacts of treatment into risk/benefit discussions. A key barrier to fully informing patients is that clinical trials in the US typically do not consider risk of financial toxicity when deciding what to test or what magnitude of benefit is needed to call a treatment beneficial.

This lack of ability to inform patients of expected impacts of therapies hinders truly informed decision-making for patients. As health care costs in the US have risen exponentially,[13] the median cost of new cancer drugs has far outpaced the costs of other therapies[14] and is accompanied by rising out-of-pocket costs,[13] directly impacting financial toxicity. These rising costs have not been accompanied by dramatic improvements in efficacy; rather, benefits of new therapies are stagnant or even decreasing as costs increase.[15] Drugs can now be approved though accelerated pathways at high costs to patients with modest improvements in intermediate endpoints, such as a 3-4% absolute improvement in invasive disease-free survival (e.g. abemaciclib in hormone receptor-positive early breast cancer); an increasing number of drugs have been approved based on high response rates (e.g. selpercatinib for non-small cell lung cancer (NSCLC)), again with unclear impact on survival. Because trials typically do not collect information on financial toxicity, these benefits may not be appropriately contextualized to allow true understanding of net benefit.

Oncology clinical trials in the US, mirroring broader trends in biomedical research funding more generally,[16] are largely funded through industry,[17] where the drive to continue to improve cancer care also feeds off a potentially dueling interest of increasing profits. These competing interests can create perverse incentives where therapeutic options, particularly drug therapies, are tested in manners where the amount of drug used is maximized. Costly new adjuvant targeted therapies after surgery are commonly given for one year (e.g. ado-trastuzumab emtansine (T-DM1) in HER2-positive breast cancer) or three years (e.g. osimertinib in EGFR-mutated (NSCLC). Efforts to identify appropriate dosing or administration length that accounts for financial impact of treatment (to patients and the healthcare system) are lacking.

A common concept in oncologic drug development is "maximum tolerated dose": the highest dose a patient can tolerate without unacceptable toxicity, which is then further investigated for evidence of efficacy. We rarely think about identifying the minimal efficacious amount of a drug to minimize financial impact of treatment.[18] Once positive trials identify a benefit to a particular therapy or dose of drug, little incentive exists to perform another study to identify a minimally effective dose that might reduce the risk of financial toxicity. In fact, a perverse incentive exists against running additional trials that may show that less drug is needed, as the very entities that typically fund these studies would stand to lose money. De-escalation trials do exist, typically funded by government agencies, but have little support and myriad challenges.

A similar perverse incentive exists within radiation oncology, where the field has favored long-course treatments due to radiobiologic concerns that were embedded into payment models connecting the number of treatments with remuneration. For example, the US has been slow to accept shorter fractionation schemes for adjuvant radiation in early-stage breast cancer despite abundant evidence suggesting safety and efficacy. Moderate hypofractionation for breast cancer has had at least five-year follow-up since 2002, when a trial[19] reported non-inferior oncologic outcomes after decreasing the length of radiation following breast-conserving surgery by 2 weeks. This was confirmed by additional trials in 2008[20, 21] and became widely used in Europe. In 2010, hypofractionation use in the US for breast cancer was <15%.[22] Consensus guidelines published in 2011[23] aided in increasing hypofractionation use, with approximately one-third of patients receiving hypofractionation in the first two years[24] and two-thirds of patients four years after publication.[25] Nevertheless, within the US' fee-for-service remuneration model, financial loss from decreasing the number of treatments was suggested to be a substantial barrier to wider adoption.[26]

Regardless of the oncologic data for hypofractionation in early breast cancer (suggesting good efficacy[19-21] and less toxicity[27]), the potential impact of fewer treatments on patients' financial well-being did not enter the discussion in consideration of adoption of hypofractionation prior to publications with a decade or more of follow-up data. A similar trend is playing out now for hypofractionation within prostate cancer.[28-30] Hypofractionation allows patients to not take additional weeks off work, pay for parking or gas,[31] pay for childcare for additional appointments, and may impact other non-paid caring roles. For some patients, this reduction in financial impact would outweigh uncertainties regarding longer-term efficacy and could help patients make appropriately individualized decisions.

The lack of consideration of financial impact is all the more concerning with increasing approval of oncology drugs through accelerated approval pathways,[32] rather than traditional pathways requiring clear impact on survival or other critical endpoints. Therapies that only show an impact on an intermediate endpoint should be subject to full evaluation of their toxicities, and the risk/benefit discussion with patients should acknowledge both that a drug may have limited impact on standard endpoints (survival, quality of life) and may impact other endpoints such as financial toxicity. Data suggests that intermediate endpoints that lead to drug approval only rarely correlate with survival,[33, 34] and many therapies (including changes in radiotherapy techniques) are adopted based on endpoints that do not correlate with survival, such as decreases in prostate-specific antigen blood levels.[35, 36] While many approved drugs later successfully complete confirmatory trials, a nontrivial minority of drugs approved via accelerated approval later fail on confirmatory trials (e.g., gefinitinib in unselected NSCLC, tositumomab in follicular lymphoma).[37] In the face of increasing costs of therapies,[14] which are likely to impact financial

toxicity,[13] the full additional risks of novel therapies (including financial risk) should be balanced with the potentially lower clinical benefit when approvals are based on unproven endpoints.

The FDA is currently undertaking a review of the accelerated approval program that bases drug approval on surrogate endpoints, which is expected to be completed in 2023.[38] This was prompted by the FDA's controversial approval of aducanumab (Aduhelm) for Alzheimer's disease.[39] In the face of increasing risk of financial toxicity with rising drug prices[14] and out-of-pocket costs,[40] combined with unclear clinical benefits,[15] the ongoing review of the accelerated approval pathway may offer an opportunity to consider the financial impact of therapy in all fields of medicine, and especially in fields like oncology, where the impact of financial toxicity has been clearly demonstrated.

Within the development of both anti-cancer drugs and other therapies, consideration of the financial impact of treatment is essential when helping patients select their best options. Improving patient-centered decision-making to include financial toxicity may improve care for marginalized and underserved populations, impact those in low/middle income countries who look to the US for guidance on best practices, and generate further work into advocacy and improving risk/benefit discussions.[41, 42] Unfortunately, our current framework of evaluation of cancer therapies, driven by clinical trials, does not prospectively obtain financial toxicity-related information. A lack of prospective collection of this data precludes the ability to share this information with patients or incorporate it into formal evaluation of trial outcomes in the way that physical toxicity risk is measured and accounted for. Of course, information collected in clinical trials will necessarily be incomplete, particularly when investigating new drugs, where typically the cost of investigational agents is borne by the study sponsor. Nevertheless, because not all financial toxicity derives from direct drug costs, clinical trials must collect information on

the impact of different approaches on financial toxicity, which can develop when treatment-related toxicity causes differences in missed work, need for domestic care resources, or additional travel for medical visits. A comprehensive framework for financial toxicity must include these indirect costs as such data are essential to complement information on the direct costs of the different regimens themselves. We must also collect information about the financial impact of treatments once translated into the "real world," especially given that not all patients have the same out-of-pocket costs associated with any particular regimen, even when drug costs are not being entirely covered by a clinical trial sponsor.

It is also essential to expand efforts to improve the value of care. Small efforts to peel back the number or intensity of therapies in a manner that may reduce financial toxicity have taken place.[43-46] Retrospective data can create hypothesis-generating data such as whether shorter durations of adjuvant therapy may offer equivalent outcomes; for example, a recent study utilizing a Veteran's Affairs population suggested that halving the length of adjuvant durvalumab after definitive chemoradiation for locally advanced non-small lung cancer might maintain excellent outcomes,[43] which may deserve further investigation. Pharmacokinetic studies identifying optimal methods of drug delivery, termed "interventional pharmacoeconomics",[47] may offer methods to test lower dosing of medications. Smaller studies have begun examining financial implications of treatment (e.g. single-institution NCT03506451). Partnership with insurance companies can result in initiatives aiming to improve quality,[44] such as promoting the use of hypofractionation, which decreases costs borne by insurers and patients alike. Novel payment methods that aim to remove fee-for-service remuneration may further change incentives that drive oncologic practices.[45, 46]

Federally funded cooperative groups can run practice-changing clinical trials, free from the perverse incentives faced by industry payers who must maintain profits. Nevertheless, de-escalation studies are challenging, often requiring large numbers of patients to power non-inferiority designs. Creative alternative approaches, including novel quantitative[48] or qualitative methods for determining non-inferiority margins that could at least in theory include the disutility caused by financial toxicity, or exploring single-arm cohort studies, merit consideration.

Cooperative groups have also begun examining the "real-world" financial impact of treatment in a manner that allows for the prospective collection of this data. For example, SWOG's CREDIT study (NCT04960787) is examining the use of financial navigation to mitigate financial toxicity. ECOG-ACRIN recently completed a study assessing financial impact of colorectal cancer treatment utilizing the Comprehensive Score for Financial Toxicity (COST)[49] measure (NCT03516942). Integration of measures such as COST with other objective measures of financial impact of cancer treatments, such as out-of-pocket costs, into trial design may add critical information that will aid us in engaging in true shared decision-making with our patients. Requiring reporting of such information during drug approval, particularly accelerated approval based on surrogate endpoints, may further build the infrastructure needed to begin prospective collection of financial toxicity data. This infrastructure will need to include both prospective collection on trials and in patients' "real world" experiences.

Furthermore, as the healthcare system engages in such efforts to mitigate financial toxicity, a concerted effort to address the embedded racial and ethnic disparities experienced by cancer patients is needed. Racial disparities in financial toxicity exist[50] yet efforts to develop measures for financial toxicity outcomes and interventions (such as financial navigation) have not typically

included a diverse cohort of patients representative of the racial and ethnic makeup within the US. For example, development of the COST measure utilized a patient population that was 74%non-Hispanic white,[49] as compared to 58% within the broader US population. Ongoing research is needed to determine optimal methods for measuring financial toxicity with a focus on developing culturally-sensitive measures to improve access and equity for underserved populations who are most vulnerable to this adverse effect. Development of these measures will further supplement efforts to prospectively measure financial toxicity outcomes.

To manage the perverse incentives of industry-funded trials within our fee-for-service remuneration system and need for ongoing clinical development, we should incorporate robust collection of financial toxicity outcomes and considerations of financial toxicity into clinical trial design and subsequent real-world evaluations, in order to allow for better understanding of the true net benefits of various treatment options and patient-centered decision-making (see Table). While small improvements in surrogate endpoints may be worth anything for some patients, for others, pursuing marginal gains may impede paying for housing or returning to work. Patients who are informed of all implications of therapy—efficacy, side effects, cost, and financial impact—are best able to engage in decision-making.

Table

Timing	Ways to incorporate financial toxicity considerations
Clinical Trials	- Fund de-escalation trials, including efforts identifying the minimal efficacious amount of drug needed or methods to increase efficiency of care delivery to reduce burden and cost to patients - Support methodological techniques that optimize the ability to conduct de-escalation efforts, such as novel methods for determining non-inferiority margins - Improve applicability of financial toxicity research by developing culturally-sensitive measures to address inequities in financial toxicity risk - Collect prospective financial toxicity information including both direct (e.g. cost of drug, supportive care) and indirect (e.g. time off work, dependent care) costs during trial conduct, using rigorous measures (e.g., COST,[49] ENRICh)
Post-marketing Surveillance	- Police completion of confirmatory trials & withdrawal of indications when necessary - Require updating financial toxicity information collected in Phase III with real-world information after drug or therapy approval

	- Incorporate collection of both direct and indirect costs in real-world settings. - Encourage research into shared decision-making to identify optimal methods to incorporate financial considerations into the informed consent process

References

1. Zafar SY, Abernethy AP. Financial toxicity, Part I: a new name for a growing problem. *Oncology (Williston Park)*. Feb 2013;27(2):80-1, 149.

2. Yabroff KR, Dowling EC, Guy GP, Jr., et al. Financial Hardship Associated With Cancer in the United States: Findings From a Population-Based Sample of Adult Cancer Survivors. *J Clin Oncol*. Jan 20 2016;34(3):259-67. doi:10.1200/JCO.2015.62.0468

3. Ell K, Xie B, Wells A, Nedjat-Haiem F, Lee PJ, Vourlekis B. Economic stress among low-income women with cancer: effects on quality of life. *Cancer*. Feb 1 2008;112(3):616-25. doi:10.1002/cncr.23203

4. Trogdon JG, Baggett CD, Gogate A, et al. Medical Costs Associated With Metastatic Breast Cancer in Younger, Midlife, and Older Women. *Breast cancer research and treatment*. 2020 Jun 2020;181(3)doi:10.1007/s10549-020-05654-x

5. Jagsi R, Pottow JA, Griffith KA, et al. Long-term financial burden of breast cancer: experiences of a diverse cohort of survivors identified through population-based registries. *J Clin Oncol*. Apr 2014;32(12):1269-76. doi:10.1200/JCO.2013.53.0956

6. Wang L, Hong BY, Kennedy SA, et al. Predictors of Unemployment After Breast Cancer Surgery: A Systematic Review and Meta-Analysis of Observational Studies. *J Clin Oncol*. 06 2018;36(18):1868-1879. doi:10.1200/JCO.2017.77.3663

7. Zafar SY, Peppercorn JM, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist*. 2013;18(4):381-90. doi:10.1634/theoncologist.2012-0279

8. Fenn KM, Evans SB, McCorkle R, et al. Impact of financial burden of cancer on survivors' quality of life. *J Oncol Pract*. Sep 2014;10(5):332-8. doi:10.1200/JOP.2013.001322

9. Zafar SY, McNeil RB, Thomas CM, Lathan CS, Ayanian JZ, Provenzale D. Population-based assessment of cancer survivors' financial burden and quality of life: a prospective cohort study. *J Oncol Pract*. Mar 2015;11(2):145-50. doi:10.1200/JOP.2014.001542

10. Ramsey S, Blough D, Kirchhoff A, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff (Millwood)*. Jun 2013;32(6):1143-52. doi:10.1377/hlthaff.2012.1263

11. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial Insolvency as a Risk Factor for Early Mortality Among Patients With Cancer. *J Clin Oncol*. Mar 2016;34(9):980-6. doi:10.1200/JCO.2015.64.6620

12. Gharzai LA, Ryan KA, Szczygiel L, et al. Financial Toxicity During Breast Cancer Treatment: A Qualitative Analysis to Inform Strategies for Mitigation. *JCO Oncol Pract*. Jul 12 2021:OP2100182. doi:10.1200/OP.21.00182

13. Keehan SP, Stone DA, Poisal JA, et al. National Health Expenditure Projections, 2016-25: Price Increases, Aging Push Sector To 20 Percent Of Economy. *Health Aff (Millwood)*. 03 2017;36(3):553-563. doi:10.1377/hlthaff.2016.1627

14. Prasad V, De Jesus K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol*. Jun 2017;14(6):381-390. doi:10.1038/nrclinonc.2017.31

15. Saluja R, Arciero VS, Cheng S, et al. Examining Trends in Cost and Clinical Benefit of Novel Anticancer Drugs Over Time. *J Oncol Pract*. May 2018;14(5):e280-e294. doi:10.1200/JOP.17.00058

16. Chakma J, Sun GH, Steinberg JD, Sammut SM, Jagsi R. Asia's ascent--global trends in biomedical R&D expenditures. *N Engl J Med*. Jan 2 2014;370(1):3-6. doi:10.1056/NEJMp1311068

17. Dogan S, Yamamoto-Ibusuki M, Andre F. Funding sources of practice-changing trials. *Ann Oncol*. Apr 1 2018;29(4):1063-1065. doi:10.1093/annonc/mdx798

18. Filloon TG. Estimating the minimum therapeutically effective dose of a compound via regression modelling and percentile estimation. *Stat Med*. May 15-30 1995;14(9-10):925-32; discussion 933. doi:10.1002/sim.4780140911

19. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst*. Aug 7 2002;94(15):1143-50. doi:10.1093/jnci/94.15.1143

20. Start Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. Apr 2008;9(4):331-41. doi:10.1016/S1470-2045(08)70077-9

21. Start Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. Mar 29 2008;371(9618):1098-107. doi:10.1016/S0140-6736(08)60348-7

22. Jagsi R, Falchook AD, Hendrix LH, Curry H, Chen RC. Adoption of hypofractionated radiation therapy for breast cancer after publication of randomized trials. *Int J Radiat Oncol Biol Phys*. Dec 1 2014;90(5):1001-9. doi:10.1016/j.ijrobp.2014.09.032

23. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys*. Sep 1 2011;81(1):59-68. doi:10.1016/j.ijrobp.2010.04.042

24. Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA*. Dec 17 2014;312(23):2542-50. doi:10.1001/jama.2014.16616

25. Woodward SG, Varshney K, Anne PR, George BJ, Willis AI. Trends in Use of Hypofractionated Whole Breast Radiation in Breast Cancer: An Analysis of the National Cancer Database. *Int J Radiat Oncol Biol Phys*. Feb 1 2021;109(2):449-457. doi:10.1016/j.ijrobp.2020.09.004

26. Marta GN, Ramiah D, Kaidar-Person O, et al. The Financial Impact on Reimbursement of Moderately Hypofractionated Postoperative Radiation Therapy for Breast Cancer: An International Consortium Report. *Clin Oncol (R Coll Radiol)*. May 2021;33(5):322-330. doi:10.1016/j.clon.2020.12.008

27. Jagsi R, Griffith KA, Boike TP, et al. Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule: Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort. *JAMA Oncol*. Oct 2015;1(7):918-30. doi:10.1001/jamaoncol.2015.2590

28. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. Aug 2016;17(8):1047-1060. doi:10.1016/S1470-2045(16)30102-4

29. Lee WR, Dignam JJ, Amin MB, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. *J Clin Oncol*. 07 2016;34(20):2325-32. doi:10.1200/JCO.2016.67.0448

30. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *Int J Radiat Oncol Biol Phys*. 07 2019;104(4):778-789. doi:10.1016/j.ijrobp.2019.03.051

31. Lee A, Shah K, Chino F. Assessment of Parking Fees at National Cancer Institute-Designated Cancer Treatment Centers. *JAMA Oncol*. Aug 1 2020;6(8):1295-1297. doi:10.1001/jamaoncol.2020.1475

32. Temkin E, Trinh J, National Organization for Rare Disorders. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. Accessed 3/25/2022, https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf

33. Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. *EClinicalMedicine*. Apr 2020;21:100332. doi:10.1016/j.eclinm.2020.100332

34. Chen EY, Haslam A, Prasad V. FDA Acceptance of Surrogate End Points for Cancer Drug Approval: 1992-2019. *JAMA Intern Med*. Apr 27 2020;doi:10.1001/jamainternmed.2020.1097

35. Xie W, Regan MM, Buyse M, et al. Event-Free Survival, a Prostate-Specific Antigen-Based Composite End Point, Is Not a Surrogate for Overall Survival in Men With Localized

Prostate Cancer Treated With Radiation. *J Clin Oncol*. Jun 2020:JCO1903114. doi:10.1200/JCO.19.03114

36. Gharzai LA, Jiang R, Wallington D, et al. Intermediate clinical endpoints for surrogacy in localised prostate cancer: an aggregate meta-analysis. *Lancet Oncol*. 03 2021;22(3):402-410. doi:10.1016/S1470-2045(20)30730-0

37. Gyawali B, Rome BN, Kesselheim AS. Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. *BMJ*. Sep 8 2021;374:n1959. doi:10.1136/bmj.n1959

38. U.S. Department of Health and Human Services. Review of the FDA's Accelerated Approval Pathway. Accessed 3/25/2022, https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp#:~:text=The%20accelerated%20approval%20pathway%20allows,to%20predict%20a%20clinical%20benefit.

39. Food and Drug Administration. FDA Grants Accelerated Approval for Alzheimer's Drug. Accessed 3/25/2022, https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

40. Ubel PA, Abernethy AP, Zafar SY. Full disclosure--out-of-pocket costs as side effects. *N Engl J Med*. Oct 2013;369(16):1484-6. doi:10.1056/NEJMp1306826

41. Fallowfield L. Participation of patients in decisions about treatment for cancer. *BMJ*. Nov 17 2001;323(7322):1144. doi:10.1136/bmj.323.7322.1144

42. Spiegelhalter D, Pearson M, Short I. Visualizing uncertainty about the future. *Science*. Sep 9 2011;333(6048):1393-400. doi:10.1126/science.1191181

43. Bryant AK, Sankar K, Strohbehn GW, et al. Timing of Adjuvant Durvalumab Initiation Is Not Associated With Outcomes in Stage III Non-small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys*. Jan 31 2022;doi:10.1016/j.ijrobp.2021.12.176

44. Jagsi R, Schipper M, Mietzel M, et al. The Michigan Radiation Oncology Quality Consortium: A Novel Initiative to Improve the Quality of Radiation Oncology Care. *Int J Radiat Oncol Biol Phys*. Feb 3 2022;doi:10.1016/j.ijrobp.2022.01.048

45. Wen L, Divers C, Lingohr-Smith M, Lin J, Ramsey S. Improving quality of care in oncology through healthcare payment reform. *Am J Manag Care*. Mar 1 2018;24(3):e93-e98.

46. Li R, Yashar C, Thaker N, Beriwal S, Glaser S. Radiation Oncology Alternative Payment Model (APM): An Introduction and Primer for the Proposed Rule for Practices and Providers. *Pract Radiat Oncol*. Jan-Feb 2021;11(1):e22-e29. doi:10.1016/j.prro.2020.04.011

47. Ratain MJ, Goldstein DA, Lichter AS. Interventional Pharmacoeconomics-A New Discipline for a Cost-Constrained Environment. *JAMA Oncol*. Aug 1 2019;5(8):1097-1098. doi:10.1001/jamaoncol.2019.1341

48. Lansdorp-Vogelaar I, Jagsi R, Jayasekera J, Stout NK, Mitchell SA, Feuer EJ. Evidence-based sizing of non-inferiority trials using decision models. *BMC Med Res Methodol*. Jan 7 2019;19(1):3. doi:10.1186/s12874-018-0643-2

49. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). *Cancer*. 02 2017;123(3):476-484. doi:10.1002/cncr.30369

50. Jagsi R, Ward KC, Abrahamse PH, et al. Unmet Need for Clinician Engagement Regarding Financial Toxicity After Diagnosis of Breast Cancer. *Cancer*. Jul 2018;doi:10.1002/cncr.31532