Appendix B
Assumptions and inputs for estimation of cost-effectiveness with inclusion of novel elements

Table of contents

B1 – Trikafta

B1.1 Dynamic pricing

- We modeled dynamic pricing by estimating post-patent reductions in drug cost across 30 patient cohorts (see B1.1.1). We assumed a constant price during a 14-year exclusivity period (see B1.1.2), then applied the post–loss-of-exclusivity (LOE) price trajectory from an IQVIA analysis (see B1.1.3). We assumed patients take the drug for 40 years (see B1.1.4).

B1.1.1 Multiple-cohort modeling

- The model includes 30 cohorts, with one new cohort entering each year.
- Cohorts are tracked concurrently. When a new cohort enters, existing cohorts remain active, and total costs and effects are aggregated across all active cohorts.
- Cohort timelines are synchronized so that survival time periods align across cohorts. See the illustration table below.

Model year	Cohort #1	Cohort #2	Cohort #3	Cohort #4	Total # of cohorts
1	✓				1
2	✓	✓			2
3	✓	✓	✓		3
4	✓	✓	✓	✓	4
…	✓	✓	✓	✓	4
40		✓	✓	✓	3
41			✓	✓	2
42				✓	1

B1.1.2 Time to LOE

- Intervention: 14 years.
- Comparator: Not applicable (no comparator drug).
- Because empirical estimates are unavailable, we assume a 14-year time to LOE.[1]

[1] Henry Grabowski 2021; PMID: 34253119; "For NMEs [new molecular entities] experiencing initial generic entry in 2017-19, the MEP [market exclusivity periods] was 13.0 years for drugs with sales greater than $250 million in 2008 dollars the year before generic entry (NMEs>$250 million), 14.1 years overall."

B1.1.3 Post-exclusivity pricing trend

- We apply post-LOE price reductions by years since LOE from an IQVIA analysis using IMS National Sales Perspectives (NSP) data (see table below).[2]

Years since LOE	Price reduction
1	66%
2	74%
3	77%
4	78%
5	80%
6	80%
7	80%
8	81%
9	81%
10	81%

- We assumed that the price reduction remained 81% constantly after 10 years post LOE

B1.1.4 Duration of drug use (Tufts calculator only)

- Intervention: 40.32 years (see A1.3).
- Comparator: Not applicable (see A1.7).

[2] Aitken 2016; https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf; Figure on page 3

B1.2 Annual productivity cost

- We used productivity cost estimates from the source CEA (Tice et al., 2020; A1). Because the study did not report annual productivity costs for both arms, we took the reported lifetime productivity cost difference (B1.2.1) and converted it to an annual equivalent (B1.2.2) for use in our calculators. We applied this annual value only to the intervention arm and assumed zero for the comparator, so the modeled difference matches the reported lifetime gap.

B1.2.1 Lifetime impact on productivity

- We estimated the lifetime productivity gains attributable to Trikafta by calculating the difference between ICER's incremental costs without productivity gains and those with productivity gains.

Quantity	Details
Incremental costs without productivity gains	Tice et al. (2020)[(a)], Table 5.9, Population 4 – Difference between costs for Trikafta plus BSC[(b)] ($7,541,000) and costs for BSC[(b)] alone ($2,224,000), or $5,317,000.
Incremental costs with productivity gains	Tice et al. (2020)[(a)], Table 5.13, Population 4 – Incremental costs of $5,234,000.
Productivity gain	$\$5{,}234{,}000 - \$5{,}317{,}000 = \$83{,}000$ reduced cost

Notes:

(a) Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, Rind DM. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, September 23, 2020. https://icer.org/wp-content/uploads/2020/08/ICER_CF_Final_Report_092320.pdf

(b) BSC is best supportive care.

B1.2.2 Conversion to annual impact

- Intervention: $3,472. We converted the lifetime impact of $83,000 (Section B1.2.1) to an annual equivalent by finding the constant yearly cost reduction whose present value equals $83,000 over the Trikafta life expectancy. As detailed in A1.3, patients have 40.32 undiscounted life years. We estimated the annual productivity gain as $PMT(3\%, 40.32, -83000, , 1)$.
- Comparator: $0. See B1.2.

B2 – Xtandi

B2.1 Dynamic pricing

- We estimated dynamic pricing effects by modeling post-patent reductions in drug costs across 30 patient cohorts (see B2.1.1). Prices were held constant during exclusivity—14 years for the intervention and 13 years for the comparator (see B2.1.2)—then followed the post-loss-of-exclusivity (LOE) trend from an IQVIA report (see B2.1.3). Treatment duration was assumed to be 1.5 years for the intervention and 1.47 years for the comparator (see B2.1.4).

B2.1.1 Multiple-cohort modeling

- We applied the same modeling assumptions described in B1.1.1.

B2.1.2 Time to LOE

- Intervention: 14 years — same rationale as the Trikafta case; see B1.1.2.
- Comparator: 13 years — approved one year earlier than the intervention, so LOE is assumed one year earlier.

B2.1.3 Post-exclusivity pricing trend

- We applied the same assumptions described in B1.1.3.

B2.1.4 Duration of drug use (Tufts calculator only)

- Intervention: 1.5 years (see A2.8).
- Comparator: 1.47 years (see A2.8).

B2.2 Real option value

- We estimated real option value (ROV) by adding potential benefits from future therapies. Using percentage changes reported in a published ROV case study for cancer drugs,[3] we applied those percentages to (1) total QALYs (see B2.2.1) and (2) total costs (see B2.2.2) for both the intervention and comparator. The case study presented two methods; we used the SEER approach because, as the authors note, "For the disease-specific mortality trend, the SEER approach can be easily generalized to other cancers."

B2.2.1 ROV multiplier: QALYs

- Intervention: 1.135 — from Li et al. (2019),[4] Table 2, appendix "Option value scenario—SEER approach," row "Ipilimumab + dacarbazine." The column "QALY gained (%)" reports a 13.5% increase after incorporating ROV, yielding a multiplier of 1.135.

[3] Li 2019; PMID: 31277824; "We estimated the cost-effectiveness of ipilimumab in 2 scenarios: a conventional scenario… and an option value scenario, where we incorporated future hypothetical improvements in mortality for metastatic melanoma owing to innovations."
[4] Li 2019; PMID: 31277824; Table 2.

- Comparator: 1.138 — calculated using the 13.5% QALY gain for the intervention and the 6.2% QALY gain applied to the incremental (delta) QALY from Li et al. (2019), Table 2, to estimate the corresponding QALY gain for the comparator.
- Let ROV_c denote the QALY multiplier for the comparator. Total QALYs were 0.73 (intervention) and 0.70 (comparator; see A2.4). Using the equation, $\frac{(1+13.5\%)*QALY\ intervention-(ROV_c)*QALY\ comparator}{QALY\ intervention-QALY\ comparator} = 1 + 6.2\%$, we calculated that $ROV_c = 1.138$.

B2.2.2 ROV multiplier: costs

- Intervention: 1.118. Value came from Li et al (2019), Table 2, Appendix labeled "Option value scenario—SEER approach," row labeled "Ipilimumab1dacarbazine." The column labeled "Healthcare cost (%)" reports a total cost gain of 11.8% after incorporating ROV.
- Comparator: 1.127 – We calculated the value using the 11.8% cost gained to the intervention and the 3.8% cost gained to the delta cost (from Li et al. (2019), Table 2) to estimate the cost gained to the comparator.
- Let ROVc denote the cost gained to the comparator; total cost was $129,769 for the intervention and $116,700 for the comparator (Appendix A2.2). We used the formula to solve ROVc: $\frac{(1+11.8\%)*Cost\ intervention-(ROV_c)*Cost\ comparator}{Cost\ intervention-Cost\ comparator} = 1 + 3.8\%$. Hence, ROVc was 1.127.

B3 – Vyndaqel

B3.1 Annual caregiver and family burden

- Intervention: $0 — assumed zero; we limited the analysis to caregiver and family burden associated with untreated disease.
- Comparator: $24,403 — calculated as caregiving time for untreated patients (0.5 week per week; see B3.1.1) × median weekly wage ($936; see B3.1.2) × weeks per year (365/7).

B3.1.1 Caregiving time

- Intervention: 0. Treated patients have substantially better functional status;[5] therefore we assumed that they do not require a caregiver.
- Comparator: 0.5 weeks. Caregivers of untreated transthyretin amyloid cardiomyopathy spent 17.5 hours per week providing care. We assumed that these hours were equivalent to half of their working week.[6]

B3.1.2 Median weekly wage

- The Bureau of Labor Statistics reported median weekly earnings of full-time wage and salary workers as $936 in 2019.[7]

B3.2 Disease severity

- We adjusted the willingness-to-pay (WTP) threshold to reflect disease severity. For untreated patients with a utility weight of 0.439,[8] we applied a 1.5-fold increase, raising the threshold from $150,000/QALY to $225,000/QALY. This approach follows established methods for severity-adjusted valuation, which suggest that traditional cost-effectiveness analyses undervalue health states with utility weights between 0.22 and 0.77.[9]

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[5] Damy 2020; PMID: 33070419; Functional capacity, as measured by the 6-minute walk test (6MWT), declined only slightly in the tafamidis treatment group (Figure 1A) and remained significantly better compared with the placebo group. The article states, "Tafamidis 80 and 20mg also both significantly reduced the decline in the 6MWT distance at Month 30 compared with placebo [least squares (LS) mean (standard error, SE) metres, 75.77 (10.08) and 75.57 (13.71), respectively; P<0.0001 for both."

[6] Ponti 2023; PMID: 37711563; Table 4, row labeled "Hours spent providing care per week, median (IQR)." column labeled "Caregivers to patients who were NYHA class III" reported 17.5 hours.

[7] BLS report; https://www.bls.gov/opub/ted/2020/median-weekly-earnings-of-full-time-workers-increased-4-point-0-percent-in-2019.htm; "In the fourth quarter of 2019, median weekly earnings of the nation's 118.3 million full-time wage and salary workers were $936"

[8] Kazi 2020; PMID: 32078382; Supplemental Table 6, column labeled "Usual Care, mean (95%UI)," row labeled "10 years" reported 0.439.

[9] Mulligan 2024; PMID: 38232447; we extracted data from "Fig. 5. Generalized risk-adjusted WTP thresholds (pooled estimates)" using plotdigitizer (https://plotdigitizer.com/) to map the 1.5-fold higher willingness-to-pay threshold for a utility value of 0.44.

B4 – Ibrance

B4.1 Real option value

B4.1.1 ROV multiplier: QALYs

- Intervention: 1.135. From Li et al. (2019). See B2.2.1.
- Comparator: 1.147 – We calculated the value using the 13.5% QALY gained to the intervention, the 6.2% QALY gained to the delta QALY (from Li et al. (2019), Table 2), the total QALY for the intervention of 2.13, and the total QALY for the comparator of 1.82 (Appendix A4.5) to estimate the QALY gained to the comparator. See Appendix B2.2.1 for the formula.

B4.1.2 ROV multiplier: costs

- Intervention: 1.118 — from Li et al. (2019); see B2.2.2.
- Comparator: 1.270 — calculated using the 11.8% QALY gain for the intervention and the 3.8% gain applied to the incremental (delta) cost per Li et al. (2019), Table 2, with total costs $372,761 (intervention) and $128,435 (comparator; see A4.2). See B2.2.2 for the formula.

B4.2 Annual productivity cost

- Intervention: $810 – The annual productivity costs associated with breast cancer (Appendix B4.2.1), adjusted by a reduction of 42% (Appendix B4.2.2).
- Comparator: $1,929. See Appendix B4.2.1.

B4.2.1 Productivity cost associated with breast cancer

- $1,929 — calculated as the annual productivity losses from breast cancer ($1,407 from work and $368 from home),[10] multiplied by 1.087 to adjust for inflation using the Consumer Price Index for All Urban Consumers (CPI-U), which was 237.017 in 2015 and 218.056 in 2010.[11]

B4.2.2 Productivity improvement from treatment

- The literature provides limited evidence on differences in productivity costs across treatments.
- We assumed the intervention drug (Ibrance) reduces annual productivity losses by 42% relative to the comparator, consistent with its hazard ratio for progression-free survival.[12]

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[10] Ekwueme 2016; PMID: 26775908; Table 3 (Total Productivity Costs of Breast Cancer for Women Aged 45–64 Years), column "Per capita productivity loss, $" reported two types of productivity loss: $1,407 for "Work loss among employed women with breast cancer" and $368 for "Home productivity loss among women with breast cancer."

[11] BLS report; https://data.bls.gov/timeseries/CUUR0000SA0?years_option=all_years

[12] Turner 2019; PMID: 26030518; "The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001)."

B5 – Eylea

B5.1 Annual productivity cost

- Intervention: Savings of $927 — calculated as 0.93 weeks saved from fewer injections (see B5.1.1) × $996 median weekly wage (see B5.1.2).
- Comparator: $0 — see next bullet.
- The source article's Table 5 ("wage loss"; see A5) reported equal productivity costs for both arms. However, that approach ignored differences in injection frequency, likely biasing the estimate. Our analysis adjusts for this bias by incorporating the time saved from fewer injections.

B5.1.1 Annual saved weeks from fewer injections

- Intervention: 0.93 workweeks saved — reduced injection frequency of 25.6 fewer injections over 11 years [13], (i.e., 25.6 ÷ 11 = 2.33 fewer injections/year) × 0.40 workweek per injection (2 days of recovery),[14] yielding 0.93 workweeks per year.
- Comparator: 0.

B5.1.2 Median weekly wage

- The Bureau of Labor Statistics reported median weekly earnings of $996 for the relevant patient population (aged ≥ 65) in 2018.[15]
- The Bureau of Labor Statistics reported median weekly earnings of $928 for the relevant caregiver population (aged ≥ 25) in 2018.[16]

B5.2 Annual family and caregiver burden

- Intervention: Savings of $864 — calculated as 0.93 workweeks saved from fewer injections (see B5.1.1) × $928 median weekly wage (see B5.1.2).
- Comparator: $0.
- Most caregivers for patients with age-related macular degeneration (AMD) are their spouses or adult children.[17] Hence, we used the median weekly wage for individuals aged 25 and older as the most representative estimate for caregiver earnings.

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[13] Brown 2020; PMID: 32565050; According to Appendix page 7 of 25, aflibercept (25.6 injections) had 25.6 fewer injections compared to bevacizumab (51.2 injections).
[14] NIH website; https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy/injections-treat-eye-conditions; "You may have short-term side effects, but they should clear up in a day or 2."
[15] BLS report; https://www.bls.gov/news.release/archives/wkyeng_07172018.htm; Table 3 row labeled "65 years and over," column labeled "Median weekly earnings" reports $996.
[16] BLS report; https://www.bls.gov/news.release/archives/wkyeng_07172018.htm; Table 3 row labeled "25 years and over," column labeled "Median weekly earnings" reports $928.
[17] Chamberlain 2025; PMID: 39990746; Table 1, section "Relationship" reported that 85% of caregivers were spouses or children, with the caregiver age range spanning from 27 to 66 years.