# Urine Detection of *EGFR* T790M Mutation in non-small-cell lung cancer: an outcomes and total cost of care analysis

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## Introduction

- Patients with EGFR mutation adenocarcinoma lung on first-line tyrosine kinase inhibitors (TKIs) eventually develop progression. About 70% develop an acquired secondary *EGFR* T790M mutation.
- Third-generation *EGFR* TKIs (3rd-gen TKIs) target T790M-positive tumors and improve outcomes.
- Standard approach for determining *EGFR* T790M mutation status after progression on a 1st or 2nd generation TKI is molecular testing of a biopsied tumor tissue specimen.
- Biopsy includes complication risks, and the median cost of hospitalization for biopsy related complications ranges from $8,908 to $15,569 (2012 USD).
- Current technology allows for the same molecular testing to be carried out in blood or urine samples.
- Circulating tumor DNA (ctDNA) fragments from cell lysis or apoptosis can be collected in urine.
- Investigators of the TIGER-X trial reported that patients with T790M-positive disease treated with a 3rd-gen TKI (rocelitinib) had similar response rates and overall survival (OS) regardless of whether positive status was detected with urine ctDNA or tissue.
- The purpose of this study is to assess the clinical and total cost of care implications of two different care pathways around detection of T790M status from a US third-party payer perspective.

## Methods

- **Tissue Testing Strategy (TTS):** Testing T790M status via biopsy only and tissue molecular genotyping.
- **Urine Testing Strategy (UTS):** Testing T790M mutation status initially by urine ctDNA. If negative, the TTS care pathway is then enacted.
- Estimated 70% of patients that progress on first line EGFR therapy harbor T790M mutation. Probability of positive, negative, and indeterminate tests for patients with T790M-positive disease, stratified by urine ctDNA or tissue, was estimated from the TIGER-X trial data.
- Median PFS with T790M-positive disease receiving subsequent therapy with a 3rd-gen TKI is 9.7 months.
- Median PFS with T790M-negative disease is 4.5 to 5 months when treated according to NCCN guidelines.
- Cost of biopsy based on analysis of electronic medical records and database of about 800 NSCLC patients on erlotinib undergoing biopsy. Mean cost of outpatient biopsy is between $1,212 and $1,584 in 2012-13 USD. Inpatient biopsies are much more expensive ($12,600 to $34,835 in 2013 USD). Costs adjusted to 2016 showed weighted cost of a biopsy $3,461 to $4,173.
- Data from 79,518 biopsies was reported from a voluntary, fee-supported database. Pneumothorax occurred in 21.4% of inpatient and 12.2% of outpatient biopsies. Hospitalization due to biopsy occurred in 21.2% of inpatients and 2.3% of outpatients.
- We estimated the proportion of outpatient biopsy to be 80.5%. Weighted average costs of managing hospitalization for pneumothorax across these three subsets of patients was $10,189.
- We implemented the base case for molecular testing to be $942 and examined the implication of parameter variation through scenario analysis.
- With UTS, the list price for the urine ctDNA test is $1495.
- We used Medicare Part B Average Selling Price (ASP) to determine the payer estimated cost of chemotherapy drugs. Based on common practice, 50% of patients were expected to receive 6 cycles of pemetrexed plus carboplatin, while the other 50% receive 4 cycles followed by 7.9 cycles of maintenance therapy with pemetrexed only.
- The cost of disease progression has been applied in other analyses of treatments for NSCLC. Estimates in this analysis are based on the total cost of care for Medicare patients with lung cancer using Surveillance, Epidemiology, and End Results Medicare (SEER) data.

**Figure 2. Full univariate sensitivity analysis (tornado diagram)**

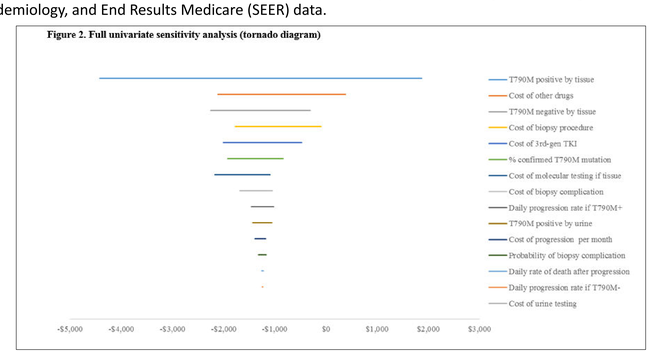
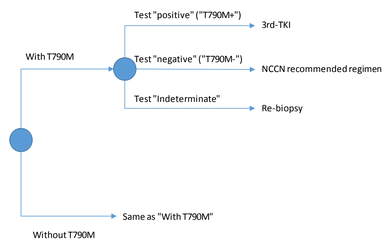
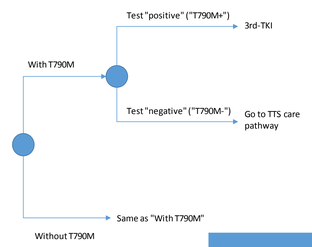



**Figure 1. Schematic of care pathways (urine testing strategy versus tissue testing strategy) for detecting T790M-positive disease**

(A) TTS care pathway




(B) UTS care pathway




| | TTS | UTS | Difference |
|---|---|---|---|
| Overall survival, mo. | 19.88 | 20.23 | 0.35 |
| PFS, mo. | 10.41 | 10.85 | 0.44 |
| | | | |
| No. biopsies | 1.10 | 0.49 | -0.61 |
| | | | |
| Costs | | | |
| Testing | | | |
| Biopsy procedures | | | |
| Truven data | $3,815 | $1,694 | -$2,121 |
| Accordino | $4,600 | $2,043 | -$2,557 |
| Complications | $676 | $330 | -$345 |
| Molecular testing | $1,039 | $461 | -$577 |
| Urine testing | $0 | $1,495 | $1,495 |
| Drugs | | | |
| 3rd-TKI | $37,547 | $40,621 | $3,074 |
| Other | $18,686 | $16,030 | -$2,656 |
| Progression | $52,065 | $51,951 | -$113 |
| Total | | | |
| Truven data | $113,827 | $112,584 | -$1,243 |
| Accordino | $114,612 | $112,932 | -$1,680 |

## Results

- Average PFS 10.41 mos with TTS and 10.85 mos with UTS (difference, 0.44 months is due to improvement in detection of T790M with UTS).
- Among a cohort of 800 patients progressed after initial treatment, 880 biopsies would be performed with TTS.
- With 80.5% of biopsies in outpatient setting, outpatient cost estimate is $830,316 - $1,138,466. Inpatient cost estimate is $2,214,599 - $2,533,501.
- Urine ctDNA testing is expected to detect 79% of the patients with T790M-positive disease. In an 800 patient cohort, we expect 392 biopsies (biopsies per patient = 0.49). Cost of outpatient biopsy is $369,868 - $507,135 and inpatient biopsy is $986,503 - $1,128,559.
- Total savings among 800-patient cohort by avoidance of biopsy is $1,688,544 to $2,036,272 (average per patient $2,111 - $2,545).
- With the lower rate of required biopsies, UTS saved cost from molecular testing ( $577 per patient) and complications ($345 per patient).
- Higher utilization of more expensive 3rd-gen TKIs in the UTS due to increased detection of T790M increases the cost of UTS treatment.
- Total cost of care per patient is an estimated $113,827 - $114,612 with TTS and $112,584 - $112,932 for UTS (savings of $1,243 -$1,680).
- UTS was cost saving over the range of input values (Figure 2). The most influential inputs on total cost of care savings were the probability of T790M positivity by tissue and the cost of treatment for test-negative patients.
- Figure 4 shows a plot of the difference between UTS and TTS in total cost of care versus the difference in PFS performed in 1000 simulations where all parameters are varied across their pre-protocol distributions. PFS and total cost of care were highly correlated (ρ = 0.882), in which a higher difference in PFS was related to a higher difference in total cost of care. This is a consequence of the cost of care increasing when 3rd-gen TKIs are appropriately administered to patients with T790M-positive disease. In over 96% of 1000 simulations, UTS increased PFS compared with TTS (Quadrants II and IV) and in more than 70% of simulations, UTS was both beneficial and cost-saving (Quadrant IV, Figure 4).

**Figure 3. Scenario analysis: cost savings of UTS based on the cost of molecular testing and the probability of patients with the somatic T790M mutation**

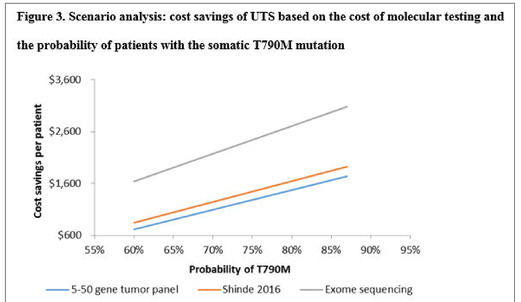
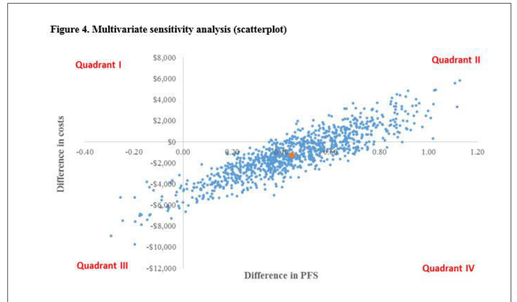



**Figure 4. Multivariate sensitivity analysis (scatterplot)**




## Conclusions

- UTS is expected to reduce biopsies and associated risk of complications by 55.6% compared with TTS.
- Cost savings exceeding $1,200 are anticipated and may be 2-to 3-fold larger (>$2700 per test ordered)
- UTS increases the likelihood of detecting T790M and treating appropriately.
- Savings significantly depend on factors including the type of treatment for T790M-negative disease. The actual cost of care is likely higher.
- Limitations:
  - Costs often vary from one setting to another, such that gathering of specific cost and complication data on a prospective population of patients is encouraged. Resource costs were derived from Medicare fee schedules, which are generally lower than costs for non-Medicare patients. Consequently, savings from avoided biopsies and their complications are likely larger than what is reported in the base case.
  - Novel technologies may have detection rates approaching 100%. As shown here, the UTS care pathway with a detection rate of about 80% is sufficient to realize considerable costs relative to TTS. The rational and efficient use of resources will necessarily put great emphasis on assigning a unit cost to the test in relation to its clinical and economic value.
- UTS is a dominant care pathway relative to TTS. It saves costs and improves the patient experience

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