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Economic impact of genomic diagnostics for intermediate-risk acute myeloid leukaemia

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Summary

Acute Myeloid Leukaemia (AML) is a rare but serious group of diseases that require critical decision-making for curative treatment. Over the past decade, scientific discovery has revealed dozens of prognostic gene mutations for AML while sequencing costs have plummeted. In this study, we compared the cost-effectiveness of multigene integrative analysis (genomic analysis) with the standard molecular testing currently used for diagnosis of intermediate-risk AML. We used a decision analytic model with data for costs and outcomes from British Columbia, Canada, to assess the long-term (10-year) economic impacts. Our results suggest that genomic analysis would result in a 26% increase in the use of first-remission allogeneic stem cell transplantation. The resulting treatment decisions and downstream effects would come at an additional cost of $12 556 [2013 Canadian dollars (CAD)] per person and the incremental cost-effectiveness ratio would be $49 493 per quality-adjusted life-year gained. Cost-effectiveness was dependent on quality of life during the long-term (5–10) years of survival, relapse rates following first-remission chemotherapy and the upfront cost of transplantation. Non-relapse mortality rates, short-term quality of life and the cost of genomic sequencing had only minor impacts. Further research on post-remission outcomes can lead to improvements in the cost-effectiveness of curative treatments for AML.

Keywords: Cost-effectiveness, genomic analysis, first remission treatment, intermediate-risk AML.

Acute Myeloid Leukaemia (AML) is a group of rare but serious diseases that progress rapidly without treatment. Curatively intended treatment is aggressive and outcomes depend on cytogenetic and molecular markers and certain clinical characteristics, such as age, initial response to therapy and concomitant diseases (Schlenk *et al*, 2008). Young adult AML patients (age <60 years) who lack significant co-morbidities are initially offered intensive induction chemotherapy. The best outcomes are achieved if induction leads to a successful first complete remission (CR1). Poorer outcomes result from a failed attempt at induction or if there is minimal residual disease after induction. If induction successfully results in CR1, a critical decision must be made for or against the use of allogeneic stem cell transplantation (CR1-SCT) to consolidate the first-remission. In most AML subgroups, treatment with CR1-SCT increases the chances of long-term survival and relapse-free survival; however, treatment-related mortality and long-term morbidity rates are higher compared to consolidation with chemotherapy alone (CR1-CHEMO) (Koreth *et al*, 2009). Some types of AML do not benefit from SCT and first-remissions may be consolidated with CR1-CHEMO without compromising the chances of a cure (Mrozek *et al*, 2007). If transplantation is not likely to be a benefit, there is also a risk that finite health care resources could be used inefficiently and direct funds away from better treatments (Drummond *et al*, 2005; Barr, 2012). These risks necessitate careful decision making when considering assignment to CR1-SCT.

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Until recently, there have been limited diagnostic tests available to inform CR1 treatment decisions. Cytogenetic and molecular analysis have been used for partial guidance towards determining prognosis in patients who are otherwise suitable candidates for CR1-SCT (Grimwade *et al*, 2010). According to cytogenetic phenotype, approximately 10% of young adult AML patients are highly likely to relapse and are most likely to be cured by treatment with CR1-SCT. Transplantation in CR1, however, does not benefit approximately 15% of AMLs who have "good-risk" cytogenetic characteristics indicating a low likelihood of relapse during post-remission years; thus, good-risk AML patients should be spared the mortality and morbidity risks associated with transplantation. Approximately 75% of the remaining AML subtypes have intermediate-risk cytogenetic characteristics and chances of successfully consolidating a CR1 are largely dependent upon the integrated effect of somatic mutations. Current National Clinical Cancer Network (NCCN) and European Society for Medical Oncology guidelines recommend diagnostic testing for three mutations in this subgroup: *FLT3*-internal tandem duplication (ITD), *NPM1* and *CEBPA* (Fey & Buske, 2013, NCCN, 2015). A poor prognosis is conferred by *FLT3*-ITD and in these cases, CR1 is best consolidated with SCT (Gale *et al*, 2008; Schlenk *et al*, 2008; Dohner *et al*, 2010). Intermediate-risk AMLs without *FLT3*-ITD that also have mutations in *NPM1* or bi-allelic *CEBPA* have an overall good prognosis. In cases where *NPM1* or *CEBPA* mutations are present and *FLT3*-ITDs are absent, patients may be spared the unnecessary risks of SCT by consolidation with CR1-CHEMO and have the same chances of a cure (Dohner *et al*, 2005; Schnittger *et al*, 2005; Thiede *et al*, 2006; Marcucci *et al*, 2008; Green *et al*, 2011).

In recent years, large-scale genomic profiling studies have identified several other mutations with evidence of prognostic value towards informing CR1 treatment decisions (Boissel *et al*, 2010; Paschka *et al*, 2010; Patel *et al*, 2012). The integrative analysis of these genes has provided unprecedented insight towards our understanding of the molecular mechanisms driving pathogenesis in AML. It is widely expected that as progress continues in genome sciences, the list of genes with diagnostic and prognostic value will continue to grow and genomic analysis will become routinely used in clinical practice in the near future (Mardis, 2011; Cancer Genome Atlas Research Network, 2013, Wetterstrand, 2015). To understand the economic effects of adopting genomic sequencing, we developed a decision analytic model that could account for the downstream treatment decisions and possible outcomes that result from genomic analysis for newly diagnosed AML. We used the model to compare the integrative analysis of ten prognostic gene mutations with standard molecular analysis of three guideline-recommended mutations. We looked at the long-term economic impact and the additional costs of the diagnostics while identifying the parameters that had the greatest influence on cost-effectiveness.

Methods

Decision model

A two-part decision analytic model was designed to account for both treatment history (such as response to induction chemotherapy or assignment to CR1-SCT) and time-dependent outcomes, such as treatment-related mortality, relapse rates and post-remission survival after initial AML treatment (Fig 1). The model starts with a decision tree comparison of genomic analysis with standard care. Both intervention and comparator arms of the analysis lead to the CR1 treatment decision node for consolidation with CR1-CHEMO or CR1-SCT. Decision tree branches terminate in Markov models for successfully consolidated first remissions. The Markov decision process takes data from the decision tree and uses time-to-event survival functions to account for costs acquired for the duration of time spent in the health state and accounts for quality of life during that time. Figure 1B shows the health states in the Markov models. Health state transitions and accumulated costs throughout the Markov models were calculated every 90 d over a period of 10 years. The model was programmed using TreeAgePro2014 (TreeAge Software Inc., Williamstown, MA, USA). Future benefits and costs were discounted by 3% annually and expressed in 2013 Canadian dollars. Years of life gained were converted to quality-adjusted life years (QALYs) using the best available evidence on health utility in the AML literature. We subtracted the sum of all costs for the standard care scenario from those in the genomic analysis scenario and divided the difference by the difference in QALYs gained to yield an incremental cost-effectiveness ratio (ICER). Individual parameters were varied independently with a one-way deterministic sensitivity analysis to test the effects of isolated parameter uncertainty. We decreased and increased health state transition probabilities and health utility values by 20%, costs by 30% and varied the discount rate between 2·5% and 5%. A probabilistic sensitivity analysis varied all parameters simultaneously over 100 000 Monte Carlo simulations to yield an estimate of combined parameter uncertainty in the model. All statistical analyses were conducted with STATA version MP12·1 (StataCorp LP, College Station, TX, USA). $P \leq 0{\cdot}05$ were considered statistically significant.

Patient data

A retrospective analysis of patient outcomes and resource utilization was undertaken following research ethics board approvals from the University of British Columbia and the Vancouver General Hospital (VGH). Outcomes such as treatment history, relapse and mortality data were derived from medical records for AML patients diagnosed between 2000 and 2011. Survival analyses with Weibull regression was applied to the outcomes data to calculate the probability of transitioning between the different health states in the model.

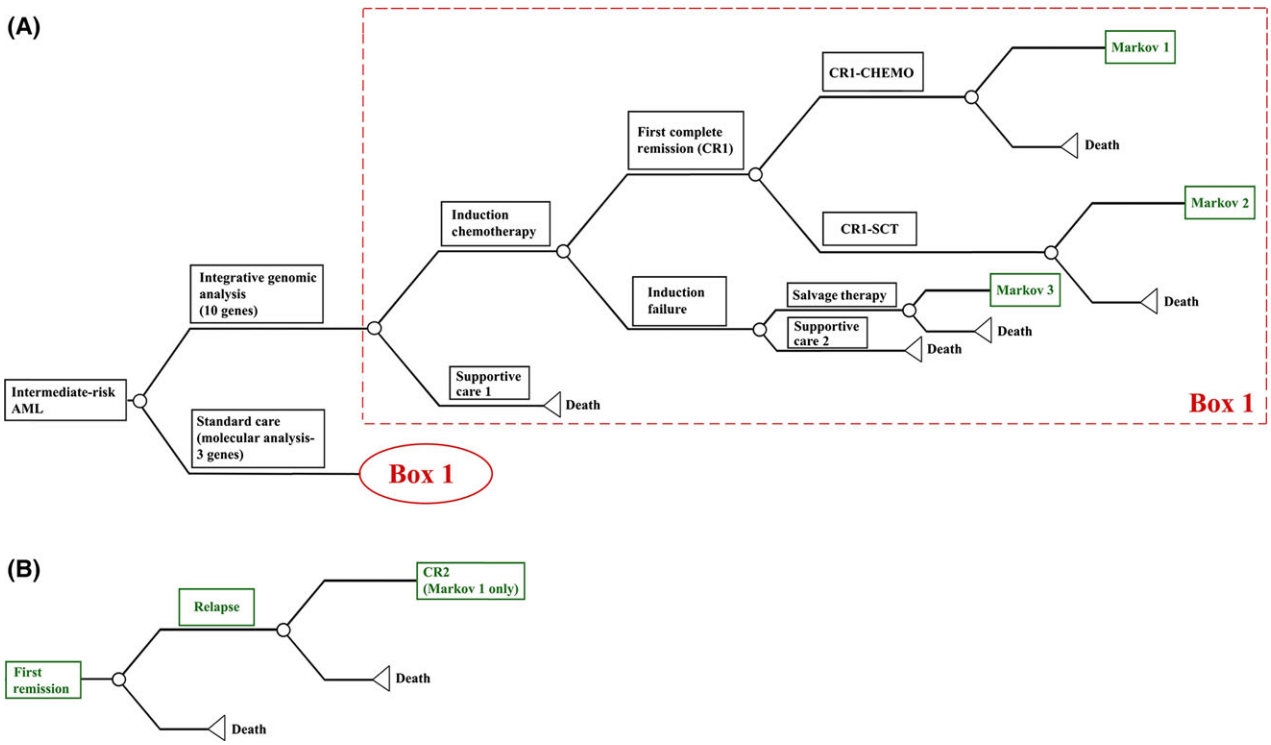

Fig 1. Decision analytic model 1A. Decision tree model of first remission induction and treatment following a complete remission in acute myeloid leukaemia (AML). Consolidation of a first complete remission (CR1) occurs by either chemotherapy (CR1-CHEMO) or haematopoetic stem cell transplantation (CR1-SCT). Transitions from consolidation therapy arrive in the post-remission Markov models that account for cumulative, 10-year costs and health state transitions over 90-day Markov cycles between relapse and death (1B). Transition to a second complete remission (CR2) is allowed following remissions consolidated with CR1-CHEMO

We included outcomes for AML patients, aged <60 years with intermediate cytogenetic risk group (Medical Research Council UK (MRC)) classification at the time of diagnosis. We excluded outcomes for patients with histological subclasses of AML that would otherwise influence CR1 consolidation decisions (*i.e.* Histological subclasses M6, APL or AML with antecedent haematological disease).

Health care resource utilization data was sampled from the same source as the outcomes data for all subtypes and ages of AML. We excluded data from patients with incomplete medical records and oversampled some patient records in order to obtain sufficient cost data (*i.e.* at least ten different patient records were sampled) for all health states throughout the model. Cost inputs were added to the individual health states according to the time from diagnosis and specific health state definitions. We included data for the following resources: inpatient and outpatient hospital days from admission/discharge records related to AML diagnosis, treatment, complications and sequelae, outpatient hospital days for blood and platelet transfusions, chemotherapy administration costs, bone marrow biopsies, lumbar punctures, stem cell donor and retrieval costs, IVIG, chemotherapy administration costs, post-transplant medicines and prophylactic post-SCT drugs. Resource utilization rates were multiplied by unit costs to determine mean, per-patient costs in 2013 Canadian dollars (CAD), (1·58 CAD ~ 1 British Pound [GBP]). Costs were grouped into individual health states and used as inputs to the model. A comprehensive description of the health states and costing methodology may be found in further detail in the supplementary material.

Scenario analysis

The standard care scenario was developed directly from the baseline outcomes data. We accounted for the number of allogeneic stem cell transplantation (alloSCT) treatments that would result from the observed and expected *FLT3*-ITD, *NPM1* and *CEBPA* mutations. The genomic sequencing scenario was built by adjusting for incidences rates that would be expected from a multi-gene stratification system and the treatment decisions implied from the integrative effect for the following select mutations: *FLT3*-ITD, *NPM1, CEBPA, IDH1/2, TET2, KMT2A* (previously *MLL)* partial tandem duplication (*KMT2A*-PTD), *PHF6, ASXL1, DNMT3A*. These mutations were selected as representative prognostic mutations based on their characterization in the AML literature of incidence rates and integrated effects. These novel mutations on CR1-SCT rates were calculated stepwise to simulate the genomic analysis scenario. If intermediate-risk AML had a poor prognosis conferred from genomic test results, CR1 was

Table I. Model inputs to the base-case analysis.

				Transition probabilities			
Health state	Markov cycle (d)	Mean cost* (SE)	Health utility†	Exit health state 1	Probability of transition to exit health state 1	Exit health state 2	Probability of transition to exit health state 2
Diagnosis	Initial (0)	$4175 (198)	0·66	Induction	0·99	Supportive care 1	0·01
Induction	Initial (0)	$38 015 (808)	0·61	CR1	0·67	Induction failure	0·31
CR1	Initial (0)	n/a	n/a	CR1-CHEMO	0·72	CR1-SCT	0·28
CR1-CHEMO	Initial (0)	$35 109 (3919)	0·66	Markov 1	0·93	Death	0·07
CR1-SCT	Initial (0)	$128 888 (8963)	0·61	Markov 2	0·94	Death	0·06
Induction failure	Initial (0)	$23 595 (3942)	0·61	Salvage consolidation	0·49	Supportive care 2	0·51
2CR1-salvage	Initial (0)	$95 912 (20 382)	0·66	Markov 3	0·8	Death	0·2
Supportive care 1	Initial (0)	$43 275 (17 333)	0·61	Death	1·0	n/a	n/a
Supportive care 2	Initial (0)	$51 812 (19 553)	0·61	Death	1·0	n/a	n/a
Markov 1	Cycle 1 (90)	$1471 (741)	0·74	Markov 1-relapse	0·20	Markov 1-death	0·00
(Remission after CR1-CHEMO)	Cycle 2 (180)	$22 (9)	0·83		0·12		0·00
	Cycle 3 (360)				0·10		0·00
	Cycle 4 (450)				0·09		0·00
	Cycle 5 (540)				0·08		0·00
	Cycles 6-40 (630 +)				<0·07		>0·01
Markov 1-relapse	Cycle 1 (90)	$73 664 (12 955)	0·50	Markov 1-CR2	0·57	Markov 1-death	0·21
	Cycle 2 (180)	$13 077 (5342)	0·30	n/a	n/a		0·32
	Cycle 3 (360)						0·38
	Cycle 4 (450)						0·43
	Cycle 5 (540)						0·46
	Cycles 6–40 (630 +)						>0·49
Markov1-CR2	Cycle 1 (90)	$87 179 (15 334)	0·66	Markov 1-CR2-death	0·11	n/a	n/a
	Cycle 2 (180)	$33 931 (14 816)	0·66		0·06		
	Cycle 3 (360)	$11 936 (5392)	0·66		0·05		
	Cycle 4 (450)	$1214 (1126)	0·66		0·05		
	Cycle 5 (540)	$696 (296)	0·66		0·04		
	Cycles 6-40 (630 +)		0·74		<0·04		
Markov2	Cycle 1 (90)	$38 254 (5164)	0·66	Markov 2-relapse	0·07	Markov 2-death	0·02
(Remission after CR1-SCT)	Cycle 2 (180)	$2799 (2435)	0·66		0·03		0·01
	Cycle 3 (360)	$888 (589)	0·66		0·02		0·01
	Cycle 4 (450)	$2516 (2388)	0·66		0·02		0·01
	Cycle 5 (540)	$9039 (6379)	0·66		0·01		0·01
	Cycles 6-40 (630 +)	$1036 (308)	0·74		<0·01		<0·01

Table I. (*Continued*)

Health state	Markov cycle (d)	Mean cost* (SE)	Health utility†	Transition probabilities			
				Exit health state 1	Probability of transition to exit health state 1	Exit health state 2	Probability of transition to exit health state 2
Markov 2-relapse	Cycle 1 (90)	$17 507 (8429)	0·30	Markov 2-relapse-death	0·52	n/a	n/a
	Cycle 2 (180)	$9057 (5961)			0·62		
	Cycle 3 (360)	$9292 (5003)			0·66		
	Cycle 4 (450)				0·69		
	Cycle 5 (540)				0·71		
	Cycles 6–40 (630 +)				>0·72		

CR1, first complete remission; CR1-SCT, consolidation with haematopoetic stem cell transplantation in CR1; CR1-CHEMO, consolidation with chemotherapy alone in CR1.
*Health state costs were applied upon entry to the health state.
†Utility was assigned from evidence available for initial treatment of myelodysplastic syndrome-progressed acute myloid leukaemia (Levy *et al*, 2014) and physician surveys for remission and relapse utility (Kurosawa *et al*, 2011).

consolidated with alloSCT from either a human leucocyte antigen (HLA)-matched sibling (SIB-SCT) or a matched unrelated donor (MUD-SCT). We applied the conservative assumption that the genomic sequencing strategy did not offer additional improvements to outcomes; the intervention arm of the analysis had different rates of CR1-SCT transitions but had the same mortality and relapse rates as the standard care arm.

The following criteria were applied to predict the change in CR1-SCT rates: Successful CR1s were consolidated with CR1-SCT from available SIB-SCT and MUD-SCT donors if a poor prognosis was conferred from the results of testing for a prognostic mutation. We then calculated the change in CR1-SCT rates. We also considered the chance that transplant-eligible patients actually receive the procedure for any reason, referencing findings from Schlenk *et al* (2008). Transplants in CR1 that did not occur for any reason were assigned to CR1-CHEMO by default.

Results

The decision model (Fig 1) accounts for both history- and time-dependent events. A summary of the baseline model input parameters that were initially applied to the model are shown in Table I. All transition probabilities were predicted with statistical significance throughout the model except for non-relapse mortality rates following CR1-SCT (Markov 2, $P = 0{\cdot}411$). The effect of this uncertainty was investigated in the deterministic sensitivity analysis and did not have an appreciable impact on cost-effectiveness due to the low frequency of these transitions (Fig 2). Short-term (<100 d) remission rates for CR1-SCT and CR1-CHEMO were similar and each consolidation approach offered a > 94% chance of transition to the Markov models. The three-year survival and relapse-free survival rates after CR1-CHEMO were significantly lower than if CR1-SCT was assigned (0·32 vs. 0·78, $P < 0{\cdot}001$ and 0·38 vs. 0·81, $P < 0{\cdot}001$, respectively).

On average, the costs associated with remissions after CR1-CHEMO (Markov 1) were lower than the costs associated with remissions in CR1-SCT (Markov 2); Long-term costs, however, were highest for treatment of relapsed disease after CR1-CHEMO. Mean costs were lower over time and highly variable during the first 2 years following an SCT. For example, 540 d after entry to Markov 2 (Cycle 5), costs were double in magnitude over the previous cycles. This reflects the cost of treating alloSCT complications, which involve lengthy hospital admissions for the subset of patients who experience the morbidity. Inpatient hospitalizations were volume cost drivers, accounting for greater than 70% of all treatment costs on average, per-patient. Further details on the cost analysis and resource utilization data may be found in the supplementary material.

In the standard care scenario, the chance of achieving CR1 from induction was 67% and CR1 was followed by transplant consolidation 36% of the time (Table II). The model

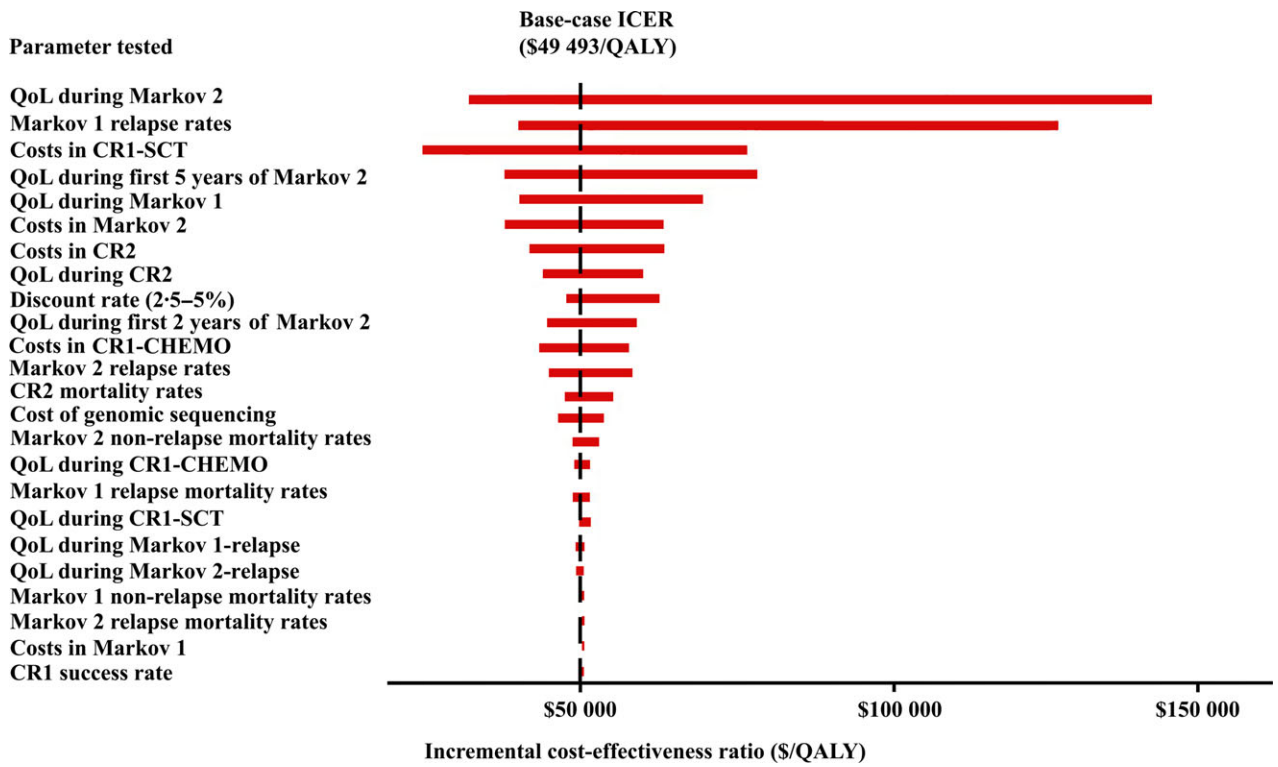

Fig 2. Deterministic sensitivity analysis**.** A one-way sensitivity analysis for select parameters to test their isolated effect on the base-case ICER, ($49 493 per QALY gained). Abbreviations: CR1, first complete remission; CR2, second complete remission; CR1-SCT, consolidation with haematopoetic stem cell transplantation in first complete remission; CR1-CHEMO, consolidation with chemotherapy alone in first-complete remission; Markov 1, post-remission survival after CR1-CHEMO; Markov 2, post-remission survival after CR1-SCT; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.

predicted that the treatment of intermediate risk-AML in the standard care arm could be expected to cost $155 503 over the full 10 years and patients could be expected to live an average 3·48 QALYs. The genomic analysis scenario increased the probability of assignment to CR1-SCT by 26% at the CR1 decision node, resulting in an additional cost of $12 556 per person and offering an additional 0·26 QALYs over the standard care arm. The incremental cost-effectiveness ratio was $49 493 per QALY. The deterministic sensitivity analysis showed that cost-effectiveness was driven by long-term health utility, rates of relapse and relapse-mortality rates after CR1-CHEMO, CR2 mortality rates, and costs for CR1-CHEMO, CR1-SCT, and CR2 (Fig 2). Cost-effectiveness was most sensitive to health utility after CR1-SCT in the 5–10 years of survival after treatment. Short-term health utility (<2 years post-remission), the cost of sequencing, costs in remission after CR1-CHEMO, non-relapse mortality rates, CR1 success rates and discounting did not have major effects on the ICER. The probabilistic sensitivity analysis showed with 58% certainty that the ICER would be considered cost-effective if the willingness to pay threshold is $100 000/QALY. This level of uncertainty was deemed acceptable considering the low incidence rate of the disease and the limited basis for economic evidence that currently exists.

Discussion

This is the first cost-effectiveness analysis to describe the long-term impacts of genomic analysis for AML. Our results, based on real-world data and conservative assumptions, suggest that the cost-effectiveness of adopting a genomic analysis strategy to inform CR1-treatment decisions does not depend on the cost of the diagnostic. If long-term effects are considered, genomic analysis would probably be considered cost-effective in most industrialized jurisdictions. The favourable ICER results from significant differences in life-years gained from CR1-SCT and marginally increased costs of CR1-SCT when compared with the additional costs associated with relapse after CR1-CHEMO. It is widely anticipated that further evidence from integrative studies will lead to improved outcomes for AML (Marcucci *et al*, 2011; Estey, 2014). Improving outcomes in the genomic analysis arm would thus improve the cost-effectiveness beyond our results that are based on the underlying conservative assumption that outcomes remain unchanged from standard care.

AML treatment costs are high and have risen more dramatically over time in comparison with most other types of cancer (Leunis *et al*, 2013a,b; de Oliveira *et al*, 2013; Wang *et al*, 2014). Our data show that the average treatment cost

Table II. Scenarios.

Scenario	Mutational test added	Number at risk for mutation*	Mutation incidence rate† (%)	Number positive for mutation (s)	CR1 success rate	Number positive for mutation at CR1	Expected change in number of MUD CR1-SCT‡	Expected change in SIB CR1-SCT	Probability of CR1-SCT versus CR1-CHEMO
Baseline data	a) *FLT3*-ITD and b) *NPM1*||*FLT3*-ITD-(tested portion of outcomes cohort)	a) 68 b) 53	a)30% b)31%	a) 20 b) 15	a) 0·45 b) 0·73	a) 9 b) 11	n/a	n/a	Baseline rate (34%)
Adjustment 1	*FLT3*-ITD (untested portion of outcomes cohort§)	156	29%	46	0·45	21	7·3	0	39%
Adjustment 2	*NPM1*||*FLT3*-ITD (untested portion of outcomes cohort§)	176	32%	55	0·73	41	0	−12·6	32%
Standard Care Scenario	*CEBPA*||*FLT3*-ITD-	194	16%	36	0·67	17	0	−5·30	Standard care rate (28%)
Scenario 1	Standard care plus *IDH1 or IDH2*-||*NPM1* + , *FLT3*-ITD-	51	3·5%	2	0·67	1·2	0	10·5	35%
Scenario 2	Scenario 1 plus *TET2*||*FLT3*-ITD-	194	8%	16	0·67	7·5	2·35	2·66	38%
Scenario 3	Scenario 2 plus *KMT2A*-PTD||*FLT3*-ITD-	194	5%	10	0·67	4·7	1·67	1·45	40%
Scenario 4	Scenario 3 plus *ASXL1*||*FLT3*-ITD-	194	4%	8	0·67	3·7	1·17	1·33	44%
Scenario 5	Scenario 4 plus *PHF6*||*FLT3*-ITD-	194	2%	4	0·67	1·9	0·59	0·67	45%
Genomic Analysis Scenario	Scenario 5 plus *DNMT3A* ||*FLT3*-ITD-	194	29%	45	0·67	30	9·32	10·5	59%

CR1, first complete remission; CR1-SCT, consolidation with haematopoetic stem cell transplantation in CR1; CR1-CHEMO, consolidation with chemotherapy alone in CR1; SIB,sibling donor; MUD, matched unrelated donor; ITD, partial tandem duplication; PTD, partial tandem duplication.

*In the baseline scenario, the number at risk for the mutation were the number tested. If mutational test positivity was conditional on *FLT3*-ITD negativity (||*FLT3*-ITD-) or *NPM1* positivity (||*NPM1* +) then *FLT3*-ITD+ counts or *NPM1*- counts were removed from the initial number at risk.

†The incidence rates and implied therapeutic decisions were reported from observed data at the Vancouver General Hospital (baseline) or calculated by referencing the literature (*FLT3*-ITD, *NPM1* and *CEBPA* (Port *et al*, 2014) in the standard care scenario; The integrated effect of: *IDH1* or *IDH2 (*Marcucci *et al*, 2011); *KMT2A*-PTD (Caligiuri *et al*, 1998; Dohner *et al*, 2002), *TET2, ASXL1, PHF6, DNMT3A,* (Cagnetta *et al*, 2014*);* was calculated based on concomitant *FLT3*-ITD negativity (Patel *et al*, 2012).

‡Number of patients at risk times the availability of human leucocyte antigen -matched sibling donors; assuming the rate of matched sibling donors available is 0·45 and the rate of transplants compliance for every available donor is 0·67 (Schlenk *et al*, 2008).

§This calculation adjusts for the incidences of *FLT3*-ITD and *NPM1* to predict the expected CR1-SCT decisions that would have occurred in the standard care arm had the entire cohort been tested for these mutations.

totals over $150 000, indicating a strong need for economic evidence for new and existing treatments. Costs in the post-remission phase can be expected to rise over the next decade as several novel drugs aimed at relapse reduction, remission maintenance or transplant bridging therapy are on the horizon (Chaturvedi *et al*, 2013; Ravandi *et al*, 2013; Johnson & Redner, 2015). High-cost therapeutics to support transplants would require greater than marginal improvements in survival or quality of life to improve the cost-effectiveness of CR1-SCT treatment. Considering that transplant costs are primarily driven by hospitalization, it is also feasible that future CR1-SCT costs could decrease as institutes become more practiced in the management of post-transplant complications.

The cost-effectiveness of genomic sequencing was most sensitive to long-term quality of life after first-remissions, yet, these data are only scarcely available for AML (Ashfaq *et al*, 2010; Barr, 2012). Patient data that incorporates preferences for individual domains on quality of life instruments would be ideal for better economic evaluations. In this analysis, health utility values were estimated from quality of life studies in AML that were either mapped to a health utility instrument from the opinions of physicians, and not patients themselves. Further study of the long-term effects with sufficient sample size and power is required in order to gain a more accurate understanding of the economic impact of CR1 treatment decisions in AML. One multicentre clinical study is underway with longitudinal health utility data results expected in the near future (NCT01685619).

The low incidence of AML is the greatest limitation on this study. In order to achieve adequate sample size our data acquisition spanned a decade. While basic treatments have not substantially changed over this time for young, intermediate-risk AML, advancements in standards of care for alloSCT have probably improved with time, which would render genomic testing more cost-effective because outcomes would be improved over what we have reported. The fundamental point of our study was to provide rationale for genomic testing which may enable greater access to patients likely to benefit from curative treatments for AML. Genomic testing, however, is only part of the sum of patient-related prognostic factors that are considered prior to assignment to CR1-SCT (Ossenkoppele & Löwenberg, 2015). With the advancement in the use of reduced intensity transplants and greater availability of alloSCT donors, the challenge of assigning an invasive, but potentially curable, treatment for patients within the 60–75 age range becomes highly individualized. For practical reasons, our analysis is also limited by the use of data from a single institution for outcomes and costs. Broader demographic study is indicated, however, multicentre studies often exclude underserved individuals. Due to the scarcity of economic evidence and high costs of treatment, multicentre studies in the future should include co-investigation with health economists and make deliberate efforts to study representative populations.

The severity and rarity of AML not only characterize the disease as a high cost cancer indication but also make it a challenging one to model (Kurosawa *et al*, 2011; Wang *et al*, 2014). The strong dependence of CR1 outcomes on early CR1 success necessitates the use of simulation methods that can account for the duration of time spent in different health states and the information presented to clinicians at the time of treatment decisions. The overall low incidence of the disease and the small subgroups contribute to low numbers of analysable data and uncertainty in the model. Economic models for AML (or most other low-incidence disease) will be further constrained by the limited availability of trial-based outcomes. Trial data for therapeutic launches, however, are susceptible to bias towards the interest of the sponsors (Sullivan *et al*, 2011). The importance of using of real-world cost and outcomes data to project population based impacts for rare diseases, such as intermediate risk AML, cannot be overstated.

Disclosures

The authors declare that they have no financial or employment interests that may be affected by the publication of this work.

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Author contributions

Contribution: S.C., A.K., D.H., and S.P. designed the research study, S.C., E.M., C.B., retrieved the data and performed the analyses, S.C., and S.P. wrote the manuscript. All authors reviewed and edited the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Patient data characteristics

Table SII. Unit costs used to convert resource utilization data into per-patient costs

Table SIII. Resource utilization and unit costs

Data SI. Health state definitions

Data SII. Cost analysis

References

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