Institution: King's College London		
Unit of Assessment: UoA1		
Title of case study: Improving Quality of Life and Survival Rates of Acute Myeloid Leukaemia (AML) Patients with Innovative Molecularly Guided Therapy		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof David Grimwade	Professor	1997 – 2016
Prof Ellen Solomon	Professor	1997 – present
Dr Richard Dillon	Clinical Senior Lecturer	2012 – present
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Acute myeloid leukaemia (AML) is a common, aggressive and frequently fatal blood cancer. King's College London has led a programme to develop and implement highly sensitive molecular tests in patients. These allow precise measurement of treatment response and thus allow therapy to be more appropriately tailored to individual patients ("molecularly guided therapy"). Our work has (a) led to changes in national clinical practice and international treatment guidelines (b) reduced the number of patients requiring bone marrow transplant (a highly toxic and expensive procedure) (c) allowed earlier detection and treatment of relapse, resulting in improved survival and quality of life for patients with this blood cancer and (d) paved the way for innovative clinical trials which are likely to further improve survival and quality of life in the future.

2. Underpinning research

AML is an aggressive form of blood cancer diagnosed in ~3000 individuals each year in the UK and ~18,000 across Europe. Currently, fewer than half of AML patients survive for more than two years after diagnosis: the leading causes of death are disease relapse and side effects of chemotherapy or bone marrow transplantation. King's ground-breaking programme of research is focussed on harnessing advanced molecular technologies to develop new diagnostic tools which can provide powerful prognostic information and permit a more personalised treatment approach. Treatment can be intensified in patients identified as being at high risk of relapse, whereas those patients who are likely to be cured can be spared from the risks of undergoing unnecessary treatment **(1)**. These tests can also rapidly evaluate responses to experimental or novel drugs both on an individual and clinical trial population level.

King's research accurately identifies patients at risk of relapse and shows that fewer patients require risky bone marrow transplant procedures. In a large clinical trial performed between 2009-2014, King's analysed 2569 samples obtained from 346 patients with AML who had undergone intensive treatment in the UK National Cancer Research Institute (NCRI) AML17 trial **(2)**. King's research showed that molecular assessment provided extremely powerful prognostic information: molecular measurable residual disease (MRD) status could split patients into two groups with dramatic differences in survival rates. Survival at 3 years was 24% for patients with, and 75% without MRD. The MRD test also significantly outperformed traditional ways of assessing relapse risk and therefore provided a much more accurate way of deciding which patients should undergo bone marrow transplantation (BMT), a procedure carrying significant risks of long-term morbidity and a 10-20% chance of treatment-related death. Importantly, the findings showed that significantly fewer patients require BMT when the MRD tests are incorporated into treatment decision making.

King's identifies a group of patients at high risk of relapse after bone marrow transplantation. Following on from this study, King's focussed on patients with a positive MRD test and therefore a high risk of relapse and studied whether having extra treatment or changes in the transplant procedure could help overcome the risk of disease relapse. This analysis defined a threshold MRD level associated with very poor outcome, identifying patients that may benefit from further treatment prior to transplantation. Moreover, King's researchers showed that a particular type of transplant (called T-replete) was associated with improved survival in this group **(3)**.

King's demonstrates that sequential molecular testing accurately identifies patients destined to relapse, allowing pre-emptive interventions to be deployed. King's showed that regularly repeating MRD tests after completion of treatment can reliably detect relapse in a subset of AML patients with Acute Promyelocytic Leukaemia (APL, accounting for 10% of AML). By incorporating molecular monitoring coupled with pre-emptive molecularly guided salvage treatment, the rate of disease relapse was reduced from 12% to 5%. Further data generated by King's in the NCRI AML17 study revealed that sequential monitoring also reliably predicts relapse in patients with non-APL AML **(2)**. In this study, all patients with either rising MRD levels or conversion from negative to positive MRD status, went on to experience clinical disease relapse. Molecular indicators of relapse occurred in patients at a median of 3 months in advance of clinical manifestations, providing a window of time that can be exploited for the delivery of pre-emptive interventions to prevent relapse.

King's develops a novel treatment that can eliminate molecular evidence of disease and prevent relapse. To exploit the window for pre-emptive intervention provided by sequential molecular testing, King's went on to test the effectiveness of a novel, non-intensive treatment (venetoclax + cytarabine) as molecularly guided salvage treatment. The data revealed a complete clearance of disease at the molecular level in 92% of patients treated with this combination, and 83% of these patients had prolonged disease-free survival **(4)**.

3. References to the research

1. Grimwade D, Hills RK. Independent prognostic factors for AML outcome. Hematology 2009. DOI: 10.1182/asheducation-2009.1.385

2. Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med 2016. DOI: 10.1056/NEJMoa1507471

3. Dillon R, Hills RK, Freeman SD, et al. Molecular MRD status and outcome after transplantation in NPM1 mutated AML: results from the UK NCRI AML17 study. Blood 2020. https://doi.org/10.1182/blood.2019002959

4. Tiong IS, Dillon R, Ivey A, et al. Venetoclax induces rapid elimination of NPM1 mutant measurable residual disease in combination with low-intensity chemotherapy in acute myeloid leukaemia. Brit J Haem 2020. doi: 10.1111/bjh.16722.

4. Details of the impact

King's work has led to the development and widespread implementation of highly accurate prognostic tools for AML patients, allowing them to receive personalised molecularly guided treatment. This has translated into changes in clinical practice, improvement in quality of life and survival and NHS cost savings. It has also paved the way for new clinical trial designs that will evaluate the effectiveness of new treatments more quickly and more accurately.

King's research changed national clinical practice and incorporated molecular MRD assessment into international AML treatment guidelines. Following publication of King's landmark study in 2016 **(2)**, molecular assessment of MRD status has now been adopted as standard of care for therapeutic decision making in patients with AML including those treated outside clinical trials. In collaboration with Guy's and St Thomas' NHS Trust, these tests have been made available for routine use in the NHS and in the past year, 5799 samples have been analysed from 1440 patients **(A)**. This represents a paradigm shift in the treatment of AML away

from a single treatment pathway towards a personalised approach in which therapy is tailored based on each individual's response to initial therapy.

Beyond the UK this change in practice has been reflected in international guidelines, for example those produced by the European Leukaemia Network **(B)** and the US National Comprehensive Cancer Network **(C)**. These guidelines are used by the majority of physicians treating leukaemia worldwide and NICE takes them into account as part of their decision-making process.

King's molecularly guided therapy advances patient survival, quality of life and long-term side effects of treatment. Improvement in patient outcome stems from (a) the ability to rationally select patients for bone marrow transplantation (BMT) and therefore to reduce the number of patients exposed to the toxicity of this procedure and (b) the ability to pre-emptively diagnose and treat relapse.

BMT has powerful anti-leukaemia activity but is associated with significant mortality and morbidity. Transplant-related mortality occurs in >10% of patients and many survivors experience serious long-term health issues particularly as a result of graft-versus-host disease (GvHD) which affects ~30% of transplant recipients. Whether to perform BMT as part of primary treatment has been controversial for many years and the decision has been based principally on risk-factors present at the time of diagnosis and clinician preference. The molecular MRD tests developed at King's have substantially refined outcome prediction and therefore allowed much more rational selection of patients for upfront BMT. Precise numbers on uptake have not yet been obtained since they are only published a few years after the treatment is finalised. However, the Chair of the National Cancer Research Institute (NCRI) Acute Myeloid Leukaemia (AML) working group estimated that ~100 patients per year can safely avoid upfront BMT in the UK alone based on King's approach **(D.1)**. Additionally, at least 5 patients per year would avoid transplant-related death and ~20 avoid the long-term morbidity associated with GvHD **(D.1)**.

Using King's serial MRD assessment approach after completion of treatment, patients destined to relapse can be reliably identified. Treating patients at "molecular relapse" rather than full-blown haematological relapse has major advantages **(D.1)**:

- Rather than requiring salvage therapy, which is conducted after the patient does not respond to standard therapy, in molecular relapse this can be timed carefully or in some cases avoided altogether. An increasing proportion of patients can receive treatment for molecular relapse as an outpatient using novel therapies such as venetoclax + cytarabine or gilteritinib, resulting in major improvements in patient experience and quality of life.
- For those patients who are treated with salvage chemotherapy in hospital, those treated at molecular relapse require fewer cycles of treatment than those treated in frank haematological relapse. It is estimated that ~25 patients per year can avoid at least one cycle of salvage chemotherapy.
- The early detection of relapse provides extra time for the identification of optimal donors for BMT and allows patients to enter salvage treatment and BMT in much better physical condition.

King's approach presents ongoing cost savings for the NHS. As well as being highly toxic, BMT is also a highly expensive procedure with NHS costs of approximately GBP100,000 per patient **(D.1)**. A reduction of 100 procedures per year therefore results in cost savings to the NHS of ~GBP10,000,000 annually. Treatment at the time of molecular relapse also results in a substantial reduction in healthcare resource use compared to treatment at frank haematological relapse. It has been estimated that 25 cycles of salvage chemotherapy are avoided each year by exploiting molecular monitoring which results in a saving of 800 bed-days as well as the associated antibiotic and blood product usage **(D.1)**.

King's led the development of emergency national guidelines and temporary new drug commissioning during the COVID-19 pandemic. During the peak of the COVID-19 pandemic it was unsafe to treat AML patients with intensive chemotherapy due to the high rates of fatality following infection, and it was desirable to reduce pressure on NHS bed occupancy. Based on their knowledge of molecular responses to novel therapies in different patient subgroups, King's researchers led the rapid development of national treatment guidelines based on the use of new drugs. This guideline was first published in late March 2020 and was updated every few weeks **(E)**.

Some of the recommended new treatments relied on the use of drugs which had not yet been approved for use in the NHS. Therefore in parallel to developing the treatment guideline, King's played a pivotal role in urgent discussions with both pharmaceutical industry partners and NHS England which led to a rapid and major change in policy to supply two novel agents (gilteritinib and venetoclax) across the NHS from April 2020 for defined patient groups for the duration of the pandemic **(D)**.

National guidelines and drug availability developed by King's were highly valued by clinicians and patients throughout the UK. An example of this is confirmed by a Consultant Haematologist at Blackpool Victoria Hospital NHS Foundation Trust in charge of a patient with AML who had an early relapse three months after the end of treatment **(F)**: "*As we identified that he had low level disease, we did not feel the need to step in with intensive chemotherapy like Flag-Ida. He therefore was able to be started on molecularly targeted treatment in the form of gilteritinib, a novel FLT3 inhibitor that has recently been approved for use. (…) This is worlds apart from Flag-Ida chemotherapy which would have required intensive inpatient treatment, with significant immunosuppression and significant risk of developing COVID. This all occurred during the height of the pandemic. I am delighted to say that he went into a second molecular remission following treatment with gilteritinib. He therefore was entirely well going into an allogeneic transplant as result of this targeted therapy. All of this could not have been achieved without the help and dedication from yourself, your laboratory and your colleges. I feel this represents truly cutting-edge treatment for acute leukaemia that is unrivalled anywhere else in Europe or indeed the world. I feel myself very fortunate to have your support and expertise on the laboratory side to help and inform my clinical decision making.*"

Another example of this is verified by a Consultant Haematologist at Leeds Teaching Hospital NHS Trust Foundation St James's Institute of Oncology **(G)** who expressed how the guidelines during the COVID-19 pandemic have been extremely helpful to him and his colleagues: *"Just writing to thank you for your help recently with the management of AML and MDS patients, specifically regarding the advised changes to management during the COVID-19 pandemic to try reduce the amount of time patients are both in hospital and neutropenic but at the same time balancing that with therapies that still provide excellent responses. (...) This has been very helpful in terms of treating patients who have molecular relapses before they get full blown relapses and for those with molecular persistence of disease markers and has also impacted in an extremely positive way the treatment pathways we are now able to offer patients*."

As of October 2020, over 350 patients have been treated using these drugs and King's is leading the collection of real-world outcome data which will inform practice in the future, including in the event of further COVID-19 waves **(H)**.

King's research paved the way for the development of novel trial designs which evaluate new drugs more quickly and accurately. Incorporation of molecular MRD measurement has provided substantial added value to the UK national AML clinical trials, allowing better understanding of effects of new treatments **(I)**. Molecular MRD status is now increasingly used as an endpoint for clinical trials because it provides a rapid read-out of treatment efficacy, while being highly correlated with traditional outcome measures such as relapse and death. King's research on MRD assessments during and following therapy have become a key element of risk stratification in many other types of AML and have been integrated into the trials to guide therapy, predict outcome and monitor for relapse. The Chief Investigator of the NCRI AML17, AML18 and

AML19 trials confirms that King's "*has been pivotal in pioneering this programme, its integration into the clinical trials and establishing MRD monitoring as a national standard of care. It is the only lab performing this work for the trials and provides a national clinical advisory service on the interpretation of the results* **(I)**."

This has led to the development of new trial designs where patients with molecular evidence of treatment failure are pre-emptively switched to alternative therapy but still counted as a failure event for the trial endpoint. An example of this design is the VICTOR trial (Venetoclax or Intensive Chemotherapy for the Treatment Of favourable Risk AML, EudraCT 2020-000273-24) **(D.1)**. This trial, which is being led by King's, is testing an original outpatient-based non-intensive treatment against standard intensive chemotherapy. Molecular MRD status is used as the primary endpoint to assess efficacy of the new combination but is also used to switch patients failing this less intensive treatment back onto standard therapy thus allowing treatment de-escalation to be safely tested without putting patients at risk of relapse. This has substantial potential benefits to patients and the NHS in terms of quality of life and resource use.

A participant from the AML17 clinical trial and patient ambassador for Blood Cancer UK said: "*I am particularly excited to be involved in the VICTOR trial which I think could offer real hope for older, less fit AML patients who might otherwise be only eligible for palliative care. Venetoclax really does seem to be offering hope for kinder, less damaging treatment. Although I remain in remission almost five years on from my transplant, I am still living with the side effects of my treatment. New drugs like Venetoclax offer real hope for successful treatment without resulting in long lasting side effects. I am very proud to be involved and support the work of Dr Dillon and his team and the AML working group* **(J)**."

5. Sources to corroborate the impact

(A) Testimonial: Operations Director, NHS London South Genomics Laboratory Hub (PDF)

(B) European LeukemiaNet Guidelines: B.1 Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424-47. [page 442, item 60]; **B.2** Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood* 2018;131:1275-91. [page 1290, item 106]

(C) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia. Version 1.2021 - October 14, 2020 [page 11, 49, 50 and 139]

(D) Sources illustrating the development of emergency national guidelines and temporary new drug commissioning during the COVID-19 pandemic: D.1 Testimonial from Chair of UK NCRI AML Working Group; **D.2** NICE - Single Technology Appraisal Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484] Committee Papers [page 16, item 10]; **D.3** NICE GUIDANCE - Gilteritinib for treating relapsed or refractory acute myeloid leukaemia Technology appraisal guidance; **D.4** NHS England interim treatment options during the COVID-19 pandemic [page 2, venetoclax / page 6, gilteritinib]

(E) Recommendations for the management of patients with AML during the COVID19 outbreak: A statement from the NCRI AML Working Party [Updated 16.6.2020]: (http://www.cureleukaemia.co.uk/page/news/523/aml-working-party-covid-19-recommendations)

(F) Testimonial: Consultant Haematologist, Blackpool (PDF)

(G) Testimonial: Consultant Haematologist, Leeds (PDF)

(H) Email from Deputy CDF Operational Lead, NHS England and NHS Improvement: Confirms >350 patients having been treated using new drugs during pandemic (JPG)

(I) Testimonial: Chief Investigator of UK NCRI AML18 and AML19 trials (PDF)

(J) Testimonial: Patient diagnosed with AML (PDF)