What is PCR?

Frequently Asked Questions

My PCR | my life

1. What is PCR?

PCR stands for 'polymerase chain reaction'. It is a diagnostic and monitoring tool used in CML to measure the response to treatment. It is not only used in CML; PCR is also used in other conditions and is generally one of or the most sensitive ways to "detect" something; for example, BCR-ABL can be detected in a person with CML, anthrax on a mailed letter, or evidence of a specific virus in a person after bone marrow transplant.

2. Why should I know my PCR level?

Every time the PCR is run the value is important, and conveniently can be compared to prior values. It often is the only test that gives someone an idea about the depth and stability of their response to treatment. A person with CML should always know their PCR level! PCR results should be explained to patients in as much depth as they can understand, so they have a good sense about the response level, how this compares to where they should be, when the next test is due and if any concern or risk has developed. ASK!

3. What does PCR measure in CML?

CML occurs when a specific change happens between chromosomes 9 and 22; parts of them swap places, creating a protein called BCR-ABL (Philadelphia Chromosome). This BCR-ABL protein is what makes leukemia blood cells different and malignant. In CML, PCR measures the amount of genetic material (called RNA or DNA) or 'blueprints' for BCR-ABL present; PCR levels are thus linked to both the amount and activity of leukemia cells remaining in someone with CML. PCR is often said to measure the residual (remaining) disease as it can detect very small levels of BCR-ABL 'blueprints'.

4. Is PCR performed from peripheral blood or bone marrow?

PCR can be performed from either blood or bone marrow samples. Having enough material to test is important so peripheral blood is almost always preferred (and a lot easier to get)!

5. Is PCR the only test I should have done during my treatment?

PCR is a powerful tool in CML, but it is not the only test needed during treatment. A bone marrow test is recommended at diagnosis to look for 'accelerated' (more aggressive) features in the marrow. A bone marrow test is also the only way to obtain the 'karyotype', where the chromosomes are examined in a number of cells to count the number with the Philadelphia chromosome (the 9:22 swap, which appears as a long chromosome 9 and short chromosome 22) or to see if any other genetic damage is visible.

The karyotype and FISH (fluorescent tagging of cells to count the number with the Philadelphia chromosome) studies are recommended to be repeated until they turn negative (this is called 'complete cytogenetic remission' — or CCyR).

Once this milestone is passed and confirmed, the PCR test is the only test that will show residual levels of CML and becomes the main way of monitoring.

6. Why is PCR important in the management of CML treatment?

PCR is a crucial tool in CML for a number of reasons; first, it is 'patient friendly', requiring a blood draw only; and second, it is a broad-ranged test, being able to measure untreated (high levels) of BCR-ABL all the way down to the lowest measurable levels.

7. How often should PCR testing be performed?

Early in treatment other tests (karyotype and FISH) may take priority over PCR; however, since the overwhelming majority of people with CML normalize their chromosome tests (karyotype and FISH) within the first 12-18 months of treatment, the PCR test becomes most important and is recommended every 3 months once further reduction in BCR-ABL levels occurs (this is referred to as moving from cytogenetic response to major molecular response). Once BCR-ABL levels have fallen at or below the major molecular response, it is recommended to keep monitoring them every 3-6 months to ensure stability and/or further reduction.

8. Should my level always be exactly the same?

No, if your PCR has changed you should not panic; there appears to be an acceptable degree of fluctuation. However, your doctor must look at your results carefully and focus on the trend overtime. In general, for a CML patient in treatment with a TKI, PCR results over time should be going down. At the beginning of treatment we expect that the PCR levels will usually go down significantly over months. Once the remission milestones are reached, the degree of reduction is generally much smaller and stability is often fine, especially when very deep remission is obtained.

A rise in PCR needs to be carefully assessed. One important consideration is the point from which the rise in PCR level occurred. For instance, a rise in PCR for a patient who was in deep molecular remission is different from an increase of the level of PCR in a patient who was not in molecular remission. Likewise, the degree of change, minimal or significant, is also an important consideration. Finally, change that leads to a loss of response, such as loss of a major molecular response, needs close assessment and often at this point, other tests should be performed.

9. What is the ideal PCR level? How long will it take to reach the ideal level of my PCR?

In CML we like to talk about achieving milestones. An important milestone is a complete cytogenetic remission (CCyR), which is very important and very protective. This is generally the equivalent to a 2-log, or 100 fold drop in the leukemia level. Additional protection clearly appears to be gained with further reduction in the PCR level to 3-logs (1,000 fold drop) or greater, referred to as a major molecular response (MMR). The MMR level of response is often referred to as a 'safe haven' below which risk of loss of response is the lowest.

This being said, the newest TKI therapies increasingly allow patients to achieve deeper responses — 4-log and 4.5-log reductions (MR4 and MR4.5). MR4.5 is the level at which measuring the PCR level is difficult in many laboratories, as it is no longer detectable or not able to be quantified. This threshold for a period of time was called 'CMR' or complete molecular remission, but based on the somewhat misleading nature of that name (as it implies complete response, which to many would mean 'zero' remaining leukemia), there is movement towards simply using the names that describe the level (MR4, MR4.5).

10. What can affect my PCR level?

PCR levels generally reflect ongoing response to treatment; there may be some variability of the shrinking volume of leukemia, and some variability in the test itself. Because it is a very sensitive test, the same patient might get a different result if measured in two different labs. Another big problem is that all labs do not use the same scale to measure and the exact same level of leukemia could result in different test results in two different labs. Great efforts are being taken to standardize PCR results and report all results on a single (International) scale. The first thing to look at if the PCR result is different from the last one is where the tests were done (same lab, different lab) and whether the international scale is being used.

Of course adherence/compliance to therapy (taking medicines for CML) is vital to stable or improving PCR results, and one of the first questions physicians and patients need to ask if the PCR level has changed is about therapy — has it been missed or stopped for any reason. Patients who stop taking their treatment daily are more likely to have higher PCR levels and, patients who miss even a modest amount of doses early in treatment are less likely to get into deep remission.

11. My last PCR has gone up. does this mean my treatment is not working?

Not necessarily, but rising PCR needs to be taken seriously. The checklist that needs to be reviewed with any change includes: the range from which the rise has been detected (in cytogenetic remission or not, in molecular remission or not), the degree of change (modest change, change leading to categorical loss of response, such as loss of MMR), and the history of the PCR stability to date. Often a rise in PCR prompts a repeat of the PCR at 4-6 weeks to see if the change is sustained and/or confirmed.

12. Should my PCR always be done in the same lab?

Ideally for now, the answer is yes. Having the PCR done in the same lab will mean reporting on the same scale, making tracking progress easier. Once all labs use the same scale (called the International Scale or IS), having the PCR done in the same lab will likely be less important and reporting will be the same globally. Efforts to have that be the case have been ongoing for many years already and hopefully it will soon be a reality.

13. What does MMR mean?

MMR is the acronym for major molecular response. MMR means there has been reduction in the PCR level to 3-logs or greater below a standard baseline (1,000x reduction). As mentioned above, the combination of achieving the cytogenetic complete remission (CCyR) milestone and the further reduction in PCR levels to MMR levels is often referred to as a 'safe haven' below which risk has been maximally optimized. MMR is the last milestone of response for which improvement in outcome has been demonstrated. This improvement in outcome is tied to reduction in risk of any loss of response as well as lowering risk of progression of the disease. At the moment, any benefits of deeper response than MMR (MR4 and MR4.5) have more theoretical benefit (related to the possibility of stopping therapy someday) than proven benefit, hence the current goal is to get all patients at least into stable MMR.

14. When should I ask for a second opinion about my CML treatment?

Anytime you want to. If there is a problem on your current treatment (side effects, response not on track, loss of response), if there is uncertainty over which medication to start with or switch to, specific or unusual side effects, etc. these are all good reasons. CML is a disease that requires long-term treatment, so you should make sure you choose a doctor that is a "good fit" for you, where you feel you can ask questions, and have an honest and open relationship. There are many CML experts who are truly passionate about working through the details and getting someone back on track, making the right decisions with people about options and explaining things so you can understand and be a part of your care journey. And they certainly want you to KNOW YOUR PCR!

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