BACKGROUND
Vascular endothelial growth factor (VEGF) is a protein that stimulates the growth, proliferation and survival of vascular endothelial cells. VEGF plays a critical role in the development of new blood vessels (angiogenesis), increases vascular permeability in small blood vessels and prevents apoptosis of vascular endothelial cells in immature blood vessels. Avastin® (bevacizumab) is a recombinant, humanized, murine, monoclonal immunoglobulin G1 (IgG1) antibody that binds all biologically active VEGF isoforms. The anti-angiogenic properties of bevacizumab have been studied in cancer patients. Given its anti-angiogenic efficacy, there is interest in use of Avastin® (bevacizumab) for ocular diseases in which neovascularization and edema play a major role. Neovascularization detected by ophthalmologists via fundoscopic examination of the retina.

Intravitreal bevacizumab was initially introduced as treatment of age-related macular degeneration. This is the indication for which Community Health Plan of Washington (CHPW) originally determined that intravitreal bevacizumab is medically necessary. High quality clinical evidence supporting the use of intravitreal bevacizumab for the treatment of additional conditions is growing. Clinical outcomes are improved with VEGF antagonists, including bevacizumab, with benefit outweighing risk in studies available to date. Bevacizumab is as least as effective as ranibizumab. Note that ranibizumab is currently covered for use in age-related macular degeneration (neovascular) and macular edema associated with retinal vein occlusion.

CHPW is expanding clinical coverage criteria for intravitreal bevacizumab, based on available high-quality scientific evidence showing improvement in clinical outcomes and benefit outweighing risk. Covered conditions mirror conditions now covered by CMS. CHPW will continue to review clinical evidence as it becomes available.

ALTERNATIVE TREATMENT OPTIONS
Alternatives to intravitreal bevacizumab for the treatment of conditions noted above include the use of another VEGF antagonist, such as ranibizumab (Lucentis) or a VEGF aptamer, pegaptanib (Macugen), laser photocoagulation for some types of neovascularization, ocular photodynamic therapy with verteporfin (Visudyne).
FDA Approved Indications and Recommended Dosing
Bevacizumab was approved by the Food and Drug Administration (FDA) in February 2004, initially to treat colorectal cancer. Approval for additional indications has occurred since then, though approval for intravitreal use has not yet taken place.

Centers for Medicare and Medicaid Services (CMS):
Medicare does not have a National Coverage Determination (NCD) for bevacizumab (Avastin). However, based on their assessment of available scientific evidence and trends in community standard use, CMS decided in October, 2009 to cover intravitreal bevacizumab for the indications proposed by CHPW (see below). See https://www.noridianmedicare.com/provider/updates/docs/Bevacizumab_avastin_use.pdf.

There are currently no Local Coverage Determinations (LCDs) for bevacizumab for the Northwest region.

TECHNOLOGY ASSESSMENT CRITERIA
- Is bevacizumab FDA approved?
  - Yes, for systemic use as chemotherapy for numerous types of cancer. It is not currently FDA-approved for intravitreal administration. As such, it is considered “off-label” for this use and is subject to local determinations.

- Does intravitreal bevacizumab improve the net health outcome?
  - Yes. Other drugs in the same category as intravitreal bevacizumab have been shown to be beneficial. Intravitreal bevacizumab has also been shown to improve vision in various eye conditions.

- Does the scientific evidence permit conclusions concerning the effect of intravitreal bevacizumab on health outcomes?
  - Yes, there are sufficient data to support the conclusions that intravitreal bevacizumab has an effect on various eye conditions.

- Is intravitreal bevacizumab as beneficial as established alternatives?
  - Yes. Head-to-head trials of intravitreal bevacizumab compared to ranibizumab (Lucentis) have not been done, perhaps in part because both are manufactured by the same pharmaceutical company (Genentech). However, other available evidence shows at least equivalent benefit to alternative therapies.

- Is improvement attainable outside investigational settings?
  - Yes. Intravitreal bevacizumab has been studied in settings outside the investigational realm. It is also being used extensively by practicing ophthalmologists and is rapidly becoming the standard of care.
CONCLUSION
Intravitreal bevacizumab was initially introduced as treatment of age-related macular degeneration. This is indication for which CHPW originally determined that intravitreal bevacizumab is medically necessary. High quality clinical evidence supporting the use of intravitreal bevacizumab for the treatment of the additional conditions is growing. Overall, the body of evidence supports the effectiveness of the therapy, with documented rapid and significant improvements in visual acuity and reduction in retinal thickness measurements over the short term (less than or equal to 132 weeks). Clinical outcomes are improved with VEGF antagonists, including bevacizumab, with benefit outweighing risk in studies available to date. Bevacizumab is as least as effective as ranibizumab. Note that ranibizumab is currently covered for use in age-related macular degeneration (neovascular) and macular edema associated with retinal vein occlusion.

This recommendation is based on available scientific evidence, satisfactory answers to the assessment criteria questions, and review by a specialist in the field. Covered conditions mirror conditions now covered by CMS. CHPW will continue to review clinical evidence as it becomes available.

This policy will be reviewed at least annually.

REQUIRED REVIEW AND APPROVALS
Intravitreal bevacizumab requires prior authorization by the CHPW Medical Director or his/her designee. Each authorization period will be for one year.

DEFINITIONS
None.

INDICATIONS/Criteria
Intravitreal bevacizumab is considered medically necessary for adults (age 18 years or older) for the following conditions:

- Diabetic retinopathy (ICD-9: 362.01, 362.02, 362.03, 362.04, 362.05, 362.06)
- Diabetic macular edema (ICD-9: 362.07)
- Retinal telangiectasia (ICD-9: 362.15)
- Retinal neovascularization NOS (choroidal, subretinal) (ICD-9: 362.16)
- Other non-diabetic proliferative retinopathy (ICD-9: 362.29)
- Retinal vascular occlusion, unspecified (ICD-9: 362.30)
- Central retinal vein occlusion (ICD-9: 362.35)
- Venous tributary (branch) occlusion (ICD-9: 362.36)
- Neovascular (wet or exudative) age-related macular degeneration (ICD-9: 362.52)
- Cystoid macular degeneration (cystoid macular edema) (ICD-9: 362.53)
- Retinal edema (ICD-9: 362.83)
- Retinal ischemia (ICD-9: 362.84)
- Rubeosis iridis (neovascularization of iris or ciliary body) (ICD-9: 364.42)
- Glaucoma associated with vascular disorders (e.g., neovascular glaucoma) (ICD-9: 365.63)
- Other specified glaucoma (ICD-9: 365.89)
- Infection by Histoplasma capsulatum retinitis (ICD-9: 115.02)
- Infection by Histoplasma duboisii retinitis (ICD-9: 115.12)
- Histoplasmosis retinitis, unspecified (ICD-9: 360.21)
- Progressive high (degenerative) myopia (ICD-9: 360.21)

Intravitreal bevacizumab is considered experimental and investigational for:
- All other ocular conditions

**SPECIAL CONSIDERATIONS**

None.

**LIMITATIONS/EXCLUSIONS**

Please refer to a product line’s certificate of coverage for benefit limitations and exclusions for these services:

<table>
<thead>
<tr>
<th>PRODUCT LINE</th>
<th>LINK TO CERTIFICATE OF COVERAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEALTHY OPTIONS</td>
<td><a href="http://hrsa.dshs.wa.gov/HealthyOptions/PDF/HOClienthandbook.pdf">http://hrsa.dshs.wa.gov/HealthyOptions/PDF/HOClienthandbook.pdf</a></td>
</tr>
<tr>
<td>WASHINGTON HEALTH PROGRAM</td>
<td><a href="http://chpw.org/assets/file/WHP_COC.pdf">http://chpw.org/assets/file/WHP_COC.pdf</a></td>
</tr>
</tbody>
</table>

**REFERENCES**

<table>
<thead>
<tr>
<th>NCQA CITATION</th>
<th>UM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFERENCES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>− Steinbrook, R. The Price of Sight – Ranibizumab, Bevacizumab, and the Treatment</td>
</tr>
</tbody>
</table>
- Ciulia TA, Rosenfeld PJ. Anti-vascular endothelial growth factor therapy for
neovascular ocular diseases other than age-related macular degeneration. Curr Opin Ophthalmol. 2009 May;20(3):166-74


<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin) for Macular Oedema Secondary to Retinal Vein Occlusion:</td>
</tr>
</tbody>
</table>
## REVISION HISTORY

<table>
<thead>
<tr>
<th>REVISION DATE</th>
<th>REVISION DESCRIPTION</th>
<th>REVISION MADE BY</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/19/2010</td>
<td>Approval</td>
<td>P&amp;T Committee</td>
</tr>
<tr>
<td>10/22/2010</td>
<td>Approval</td>
<td>P&amp;T Committee</td>
</tr>
<tr>
<td>03/07/2011</td>
<td>Revision to include additional indications</td>
<td>Lucy Sutphen, MD, FACP</td>
</tr>
<tr>
<td>03/24/2011</td>
<td>Approval</td>
<td>P&amp;T Committee</td>
</tr>
</tbody>
</table>